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ACUTE AND SUBACUTE CORONARY INSUFFICIENCY*

BY

PAUL WOOD, O.B.E., M.D., F.R.C.P.

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The term "acute coronary insufficiency" has become increasingly familiar since it was properly described as an entity by Master and his colleagues in 1947. It may be defined as a state in which the coronary circulation is insufficient to meet the full metabolic demands of the myocardium at rest, yet sufficient to prevent myocardial infarction. The modified title of this paper was chosen to emphasize the prolonged course of the illness in one-half of the patients. Thus in the 150 cases studied the illness was acute, lasting less than six weeks, in 50%; subacute, lasting between two and six months, in 45%; and chronic in 5%.

Characteristically this transient physiological state arises spontaneously during the course of ischaemic heart disease due to occlusive coronary atherosclerosis. Special forms of coronary insufficiency may be associated with paroxysmal tachycardia, paroxysmal atrial fibrillation or flutter, severe haemorrhage or shock, asphyxia, hypertensive crises, ruptured aortic cusp, spirochaetal aortitis, severe anaemia, and several other conditions; but these are beyond the scope of this paper. I am concerned here entirely with coronary insufficiency as it occurs in ischaemic heart disease.

My immediate purpose is to draw greater attention to this syndrome and its frequency, to redescribe its clinical features for the benefit of those who are still unfamiliar with it, to offer factual data concerning its natural course, and especially to record the results of anticoagulant therapy.

Material

The analysis is based on a consecutive series of 150 cases seen over a period of about 10 years at the National Heart Hospital, at the Brompton Hospital, and in private practice. The diagnosis was made from the clinical history, negative physical signs, characteristic electrocardiogram, and absence of laboratory data denoting fresh infarction. In most cases attacks of angina were witnessed and in many an electrocardiogram was also recorded when pain was present.

The average age of these 150 patients was 56, and the male:female sex ratio was just under 3:1. The total duration of ischaemic heart disease when the patient was first seen averaged 3.7 years, previous cardiac infarction had occurred in 25%, and the electrocardiogram provided conclusive proof of ischaemic heart disease in 87%.

*Presented at the joint meeting of the British and Canadian Medical Associations in Edinburgh on July 21, 1959.

Prevalence

The true incidence of coronary insufficiency is difficult to determine. Some idea of its prevalence, however, may be gathered from the following data:

1. In a consecutive series of 1,000 cases of ischaemic heart disease seen privately over the past 10 years the presenting feature was acute or subacute coronary insufficiency in 10%, simple angina pectoris in 30%, fresh cardiac infarction in 24%, and old cardiac infarction with or without angina pectoris in 36%.

2. According to Mounsey (1951), one-quarter of all cases of acute cardiac infarction have warning symptoms indicating a preliminary state of acute coronary insufficiency. In a consecutive series of 100 cases of cardiac infarction under my care the major attack was preceded by a state of acute coronary insufficiency for an average period of 3.3 weeks in 45%. In two-thirds of this group the warning period did not exceed three weeks. Information is not available concerning the frequency of acute coronary insufficiency preceding sudden death from acute cardiac infarction.

3. Conversely, 22% of 50 cases of acute or subacute coronary insufficiency that were treated conservatively in the present series developed frank cardiac infarction within two months of the day the diagnosis was made (first consultation).

Pathology

There was virtually no necropsy evidence concerning the pathology of acute coronary insufficiency in the present series. Most deaths followed the clinical development of cardiac infarction, and this was proved at necropsy in seven instances, the infarction being due to coronary thrombosis.

Sudden death from ventricular fibrillation during acute coronary insufficiency occurred in only 2.6% of 150 cases, and a post-mortem examination was not carried out in these four cases.

Seven patients died after a prolonged period of subacute or chronic insufficiency (three months to two years), and, although advanced occlusive coronary disease with old thrombosis and cardiac infarction was usually found at necropsy, there were two instances in which neither thrombosis nor previous infarction could be demonstrated.

The clinical data, however, support the view that acute coronary insufficiency is due to coronary thrombosis without infarction. In the present series the onset was sudden in 81%, gradual deterioration of previous angina pectoris over a period of three to six months

occurring in only 19%. Even more convincing was the fact that 20% of the series not only developed acute coronary insufficiency abruptly, but did so at a time when they seemed to be in perfect health, entirely free from symptoms, and with no previous history of angina pectoris. It is difficult to believe that anything short of coronary thrombosis could so impoverish the coronary circulation so suddenly.

Until reliable necropsy data become available, it is reasonable to assume that cases with an abrupt onset have had a fresh coronary thrombosis, and that cases with angina pectoris which gradually deteriorates until it reaches a state of coronary insufficiency at rest may be attributed to progressive occlusive atherosclerosis alone.

The Clinical Syndrome

Characteristically, as just stated, the onset of acute coronary insufficiency is sudden, a state of normal health (20%) or of relatively mild angina of effort, with or without a previous history of cardiac infarction, changing abruptly to one of almost total incapacity. Although the pain is usually provoked by all the familiar triggers, including changes of temperature, a meal, getting into bed at night, or getting up in the morning, as well as by trivial effort and excitement, it may also occur spontaneously when the patient is sitting quietly in a chair reading the paper, or may wake him repeatedly from sleep.

The attacks tend to be prolonged, often lasting between 10 and 30 minutes, but are usually shortened by trinitrin. Sometimes, however, trinitrin brings indifferent relief. Indeed, if more than two tablets of trinitrin are consumed one after another, because of this indifferent relief, the pain may increase and in more than one instance syncope has resulted.

These unprovoked attacks of angina pectoris occur at varying intervals over a period of days, weeks, or months. In some cases the patient is remarkably well in the intervals between the attacks, being able to walk freely on the level without discomfort, and in rare instances even strenuous effort fails to provoke pain.

That the pain is cardiac, however atypical its behaviour, is usually obvious on account of its central position in the thorax, its radiation to the arms or jaws, and its constricting or oppressive quality. In the great majority there are no abnormal physical signs, although the blood-pressure may be raised if taken during an attack of pain, and closure of the aortic valve may be delayed (reversed split second sound).

The electrocardiogram, however, is diagnostic in 80% of the cases, showing widespread ischaemic depression of the S–T segment when recorded at rest between attacks. In the present series a further 8% showed evidence of previous cardiac infarction only, and in 12% the graph was strictly normal. An ischaemic graph taken during an attack of pain confirms the diagnosis of angina pectoris, but, of course, does not then prove a state of acute coronary insufficiency.

A diagnosis of acute coronary insufficiency denies evidence of cardiac infarction. Thus there is no fever, leucocytosis, or rise of the erythrocyte sedimentation rate; the C-reactive protein test is negative; and both the serum glutamic oxalacetic transaminase level and the lactic dehydrogenase activity remain normal.

It must be admitted, however, that the physiological situation in these cases is critical, and that the gap between acute coronary insufficiency and cardiac infarction is narrow. After prolonged attacks minor degrees of necrosis may occur and cause transient or repetitive T-wave inversion in serial electrocardiograms, and perhaps slight changes in the laboratory data mentioned. These should be regarded as borderline cases.

Course

The natural course of acute coronary insufficiency was studied in 50 patients treated conservatively. These patients received rest, a low-calorie and low-fat diet, trinitrin as required, and often pentaerythritol tetranitrate in doses of 10–30 mg. t.d.s.

As stated in the introduction, the duration of acute coronary insufficiency is less than six weeks in 50% of the cases, but in the other 50% the illness proves to be subacute or chronic. Thus it lasted for two to three months in 30% of the present series, from four to five months in 15%, and for appreciably longer than this, even up to two or three years, in 5%. The duration of acute or subacute coronary insufficiency was little influenced by treatment when the course was not terminated by cardiac infarction or death.

Cardiac infarction occurred within two months of the onset of acute coronary insufficiency in 11 of these 50 untreated patients. Eight of them died. Seven other patients died when in a state of subacute or chronic coronary insufficiency: two from cardiac infarction, two abruptly, two in their sleep, and one from cerebral thrombosis. Thus the total mortality was 30%.

When the course was favourable attacks of pain gradually abated, and after a variable interval patients usually regained their previous state of health.

The after-histories of the 35 patients who survived the attack of coronary insufficiency may be summarized as follows: 10 could not be traced; nine died in an average period of four years either from cardiac infarction, suddenly from angina pectoris, or after they had relapsed into a state of coronary insufficiency; six had a recurrence of acute coronary insufficiency or developed subsequent cardiac infarction within five years (usually within one year); one relapsed into a state of chronic coronary insufficiency and is still alive; seven are relatively well with mild or moderate angina of effort; and two are symptom-free. Thus only 26% of the survivors are known to have done relatively well for an average period of five years (range three to seven years); a similar percentage are dead and 20% have suffered further coronary episodes.

If we assume that the untraced patients fared similarly to those that were followed up, then roughly one-third of the initial survivors are dead, one-third have had recurrent coronary episodes, and one-third are relatively well. This is a sinister record for an average period of about five years. It must also be remembered that many cases of acute coronary insufficiency are not classified as such because they are not seen until they have already developed cardiac infarction.

Anticoagulant Treatment

A series of 100 patients with acute coronary insufficiency were treated with phenindione ("dindevan"), or occasionally with ethyl biscoumacetate ("tromexan") or nicoumalone ("sinthrome"), and the more severe cases also received two or three initial injections of 12,500 units of heparin intramuscularly

over the first 24 hours. The initial dose of phenindione was 50 mg., repeated 12-hourly for five doses. Subsequent doses varied according to the prothrombin time, which was maintained between 2 and 2½ times the control time (ratio 2–2.5 : 1).

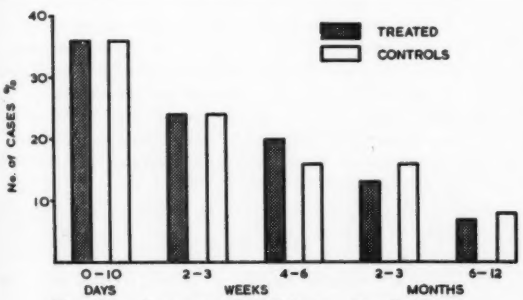
In the earlier cases treated between 1947 and 1953 anticoagulant therapy was nearly always withheld when the patient had recovered from the coronary insufficiency episode, but was always continued for a minimum of six weeks. Since then, however, an increasing number of these patients have remained on permanent anticoagulant therapy, and this is now routine practice.

The results of anticoagulant treatment in this series of 100 cases were compared with those obtained in 50 similar controls. During the first two years of the period of study alternate patients with acute coronary insufficiency received anticoagulant therapy, and alternate patients served as controls. It soon became obvious, however, that the controls were faring worse than the treated cases, and it became morally difficult not to offer all patients the protection that anticoagulant treatment seemed to give. Thus the last 30 patients in the control group were not chosen at random, but for some particular reason, such as a recent history of peptic ulcer, previous haematemesis, a tendency to spontaneous bruising, geographical difficulty, prejudice on the part of the general practitioner or other consultant concerned in the case, or for some other reason of this sort. In all other respects, however, the cases in the control group were precisely the same as those treated. Table I shows that the average age of the patients, the sex ratio, the total duration of ischaemic heart disease, the frequency of cases seen within the first three weeks, and the frequency of ischaemic depression of the S–T segment of the electrocardiogram were virtually identical in the two groups. Previous cardiac infarction and intermittent claudication occurred a little more commonly in the treated patients.

Perhaps the most important condition in making a comparison of this kind is that the time interval between the onset of acute coronary insufficiency and the day the patient was first seen should be the same in each group. The Chart shows that the percentage of treated and untreated cases seen within 10 days of the onset, within two to three weeks, within four to six weeks, and at longer intervals. It will be seen that in respect of these time intervals the two series were remarkably similar.

TABLE I.—*Coronary Insufficiency in 100 Cases Treated with Phenindione and 50 Controls*

	Treated Cases	Controls
Age	56	56
M : F sex ratio	2·9 : 1	3 : 1
Total duration ischaemic heart disease (years)	3·7	3·8
Duration of coronary insufficiency:		
Average (weeks)	4·3	5·4
Up to 3 weeks	60%	60%
Previous infarct	29%	18%
Claudication	12·5%	7%
Ischaemic E.C.G.	80%	75%
Old C.T. only	8%	9%
Normal E.C.G.	12%	16%



Duration of coronary insufficiency when first seen.

The results of anticoagulant therapy are compared with those of conservative management in Table II, and may be summarized as follows: (1) The mortality of treated cases was one-fifth that of the controls. (2) The percentage of cases that failed to improve and finally entered a state of chronic coronary insufficiency when treated with anticoagulants was one-third of the number that behaved in this way when not so treated. (3) Cardiac infarction within two months of starting treatment was seven times less common in the group given anticoagulants than in the group managed conservatively (3% compared with 22%). (4) When cardiac infarction occurred while the patient was under observation for acute or subacute coronary insufficiency, the mortality was 66% and was similar in both groups. (5) Neither cerebral thrombosis nor ventricular fibrillation occurred in the treated cases, but accounted for three deaths in the controls. (6) Two of the treated patients developed cardiac infarction within a week or two of anticoagulants being withheld. (7) Good results, the patients returning to work and leading a useful life with or without relatively mild angina pectoris, occurred more than twice as often in cases treated with anticoagulants as in the controls (75% compared with 32%).

TABLE II.—*Acute Coronary Insufficiency in 100 Cases Treated with Phenindione and 50 Controls*

Results	Treated Cases %	Controls %
Good	75	32
Infarct within 2 months	3 (2 died)	22 (16 died)
,, after withholding anticoagulants	2 (1 ,,)	
Chronic coronary insufficiency	9 (3 died)	22 (8 died)
Cerebral thrombosis	0	2 (died)
Ventricular fibrillation	0	4 (,,)
Deteriorated and anticoagulated		4
Untraced	9	14
Minimum mortality	6	30

These results bear out preliminary impressions gained from a smaller series reported 12 years ago (Wood, 1948), and are in harmony with the experience of Nichol (1950), who reported two infarcts in a series of 41 cases of acute coronary insufficiency treated with anticoagulants (no controls). Beamish and Storrie (1960) treated 85 cases with anticoagulants, and only two of them developed cardiac infarction; of their 15 controls infarcts occurred in all but one, and 11 proved fatal. In a series of 158 similar cases observed by Levy (1956), all of which were managed conservatively, frank cardiac infarction developed in 23.4%. The total mortality in his series was 32.3%, 15.8% dying from ventricular fibrillation and 16.5% from cardiac infarction. Thus as many as 70% of his patients who developed cardiac infarction died. These figures relating to the natural course of this unstable and dangerous state are remarkably similar to those reported here.

Subsidiary Treatment

Bed rest and a diet low in calories and animal fat formed a routine part of the treatment. A cardiac bed or special armchair was used when patients tended to have angina when lying flat. One patient was often

forced to stand to obtain relief from pain. Sedatives were given as required, and pethidine was sometimes administered in the early stages when pain was severe.

Contributory factors, such as diabetes mellitus, hypertension, and obesity, were corrected so far as was possible. Cases with serious hypertension, however, were not included in the series analysed.

The only coronary vasodilators that were used in this study were trinitrin, p.r.n., and pentaerythritol tetranitrate, in the form either of "peritrate" (10 mg.) or of "myocardol" (30 mg.), in doses of one or two tablets three times a day, one hour before meals.

Adverse blood lipid patterns that did not respond to diet alone were countered with 40–50 oz. of corn oil daily or with nicotinic acid, the dose of which was gradually increased from 100 mg. t.d.s. to 500 t.d.s., if well tolerated. Such treatment was rarely given unless the serum cholesterol remained obstinately high, between 350 and 700 mg./100 ml., and was uninfluenced by the decision to give anticoagulants or not. Neither triparanol ("MER-29") nor oestrogens were used in this series.

During 1958 iproniazid ("marsilid") proved helpful in relieving intractable cardiac pain in states of coronary insufficiency, but did not influence the fundamental course of the disease (Towers and Wood, 1958). The hypotensive, anabolic, hepatotoxic, and neuromuscular side-effects of iproniazid, however, limited its use. During the last two years other mono-amine oxidase inhibitors relatively free from these side-effects have been tried, particularly isocarboxazid ("marplan"), but on the whole they have been less effective. It is repeated for emphasis that these substances do not alter the fundamental course of the disease. They are best used temporarily, to overcome undue suffering when the patient is incapacitated, and should usually be withheld before he returns to work, for masking angina pectoris may be dangerous.

Summary

The clinical features and natural course of acute coronary insufficiency are described.

The results of anticoagulant therapy in 100 cases are compared with those of conservative management in 50 cases.

Cardiac infarction developed within two months in 3% of the treated cases and in 22% of the controls.

The mortality of treated cases was one fifth that of the controls.

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A new edition of *Introductory Manual on the Control of Health Hazards from Radioactive Materials* has now been published in the Medical Research Council's regular series of Memoranda. As the preface to the volume indicates, it is essentially an introductory manual intended mainly for the guidance of those concerned with the manipulation of radioactive materials in laboratories and elsewhere. Publications dealing in greater detail with various aspects of hazards from radiation are mentioned in the text and in the bibliography. (H.M.S.O., M.R.C. Memorandum No. 39, price 1s. 9d. net.)

MORTALITY FROM PRIMARY TUMOURS OF BONE IN ENGLAND AND WALES

BY

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The suggestion that small doses of radiation might be capable of inducing cancer has stimulated interest in the incidence of some of the rarer forms of the disease. In particular, it has been suggested that the very small amounts of radium and other radioactive substances which are located in the skeleton might be responsible for some cases of bone tumour, and that the incidence of such tumours might vary from one geographical area to another, depending upon the radioactivity of local food and water supplies (Marinelli, 1958). Experiments have shown that large doses of radioactive substances will regularly cause bone tumours in a high proportion of animals (Brues, Lisco, and Finkel, 1946; Finkel, 1956), and observations on patients given deep *x*-ray therapy (Vaughan, 1956), and on persons exposed to radium therapeutically or in the course of their work (Martland, 1931; Aub, Evans, Hempelmann, and Martland, 1952; Looney, Hasterlik, Brues, and Skirmont, 1955; Looney, 1956) have demonstrated that ionizing radiations can also cause bone tumours in man. It does not follow, however, that a similar effect will be produced by smaller doses, and it is possible that very small doses will not produce any risk of cancer at all.

The maximum effect of small doses can be estimated by assuming (1) that the effect is proportional to the dose, and (2) that the total natural incidence of cancer is attributable to natural background radioactivity. This method was used by the United Nations Scientific Committee on the Effects of Atomic Radiation (1958) to estimate the maximum amount of bone cancer which might be due to the ingestion of very small quantities of strontium-90 and of other radioactive substances; but they thought it reasonable to assume that not more than 10% of primary bone tumours could be attributable to natural radioactivity. They assumed that the annual incidence of primary bone tumours was between 5 and 10 cases per million persons per year, and they therefore made their calculations on the basis that "a natural radiation level of 9 rem per 70-year human lifetime" would give rise to between 5 and 10 cases per million persons in a 10-year period.

One of the many difficulties in making this type of calculation is that there is no accurate measure of the incidence of bone tumours. The disease is rare and data collected from cancer registries relate to too short a

*Since the completion of the work Dr. Mackenzie has died.

period or to too small a population to provide a reliable estimate of incidence. Mortality data are available for larger populations; but, in this instance, the certified cause of death is thought to be often insufficiently accurate. For example, the death rate attributed to primary bone tumours in England and Wales fell between 1947 and 1957 from 28 per million men to 16 per million and from 17 per million women to 12 per million. There is no reason to suppose that the true incidence of the disease fell during this period, and it seems likely that the change in the recorded mortality was largely due to the more accurate diagnosis of other types of cancer presenting with metastases in bones.

The present study was therefore undertaken, at the request of the Medical Research Council's Committee on Protection Against Ionizing Radiations, to obtain a more reliable estimate of the mortality from bone tumours in this country. It was realized that mortality would, at best, give only an indirect estimate of incidence; but, in the absence of any dramatic change in the efficacy of treatment, it seemed reasonable to use mortality rates as an indication of a change in incidence with time or of a difference in incidence between different areas. Since it was proposed to obtain data for an entire population, it was hoped that the results would also provide reliable comparisons of the impact of the various types of tumour in men and in women at different ages.

Method

The General Register Office has extracted records of all deaths attributed to malignant tumours of the bone (No. 196 in the International Statistical Classification of Diseases, World Health Organization, 1949) which occurred in England and Wales in the three years 1951–3 among persons aged under 65 years. Persons aged 65 and over were excluded, as it was thought that the proportion in which the cause of death had been adequately investigated would be too small for the purpose of the present inquiry. Three years were studied, to provide enough data for analysis by sex and age and by the site of the affected bone, and these particular years were chosen because 1951 was the earliest year for which suitable records were still available and 1953 was the year in which the first megaton hydrogen bomb was exploded and the stratosphere was contaminated with appreciable amounts of fission products.

From the death entry, information was obtained about the sex and age of the patient, the place of death, the usual place of residence, and the occupation. The certified cause of death was also copied in full. If the case had been registered in the national cancer registration scheme and details of the basis of the diagnosis were available, the details were extracted from the records. If not, and the patient had died in hospital, the hospital was written to and inquiries were made about (1) the final hospital diagnosis; (2) whether the diagnosis had been made at necropsy or operation, or, if not, the nature of the evidence on which the diagnosis had been based; and (3), if a microscopical examination had been made, the nature of the histological report. If there was no evidence that the patient had attended hospital, the doctor who signed the death certificate was asked whether the diagnosis had been made after investigation in a hospital. If so, he was asked the name of the hospital and the approximate date of attendance; if not, he was asked to give the evidence on which the diagnosis was based.

The cases in which additional information was obtained were reviewed individually by us and were classified in three groups according to the certainty and nature of the diagnosis: (1) satisfactory evidence of a primary bone tumour; (2) satisfactory evidence that the condition was not due to a primary bone tumour; and (3) evidence of presence or absence of a primary bone tumour uncertain. Cases with histological evidence of the type of tumour were classified in seven groups—that is, osteosarcoma, chondrosarcoma, fibrosarcoma, giant-cell tumour, chordoma, Ewing's tumour (including angio-endothelioma), and other or unspecified sarcoma.

In general, the hospital discharge diagnosis was accepted as the final diagnosis unless (1) it appeared to relate to an irrelevant admission and was clearly unrelated to the cause of death, or (2) there was additional and unequivocal evidence that another diagnosis was preferable — for example, necropsy evidence or a conclusive histological report which appeared not to have been taken into account. If the hospital diagnosis was itself uncertain—for example, ? sarcoma, ? secondary carcinoma of the ilium—or the hospital report provided conflicting evidence, the diagnosis was classified as uncertain. Diagnoses referring to sarcoma of a part of the body without specifying a bone—for example, sarcoma of thigh—were regarded as relating to soft-tissue tumours so long as the rest of the evidence was consistent with this diagnosis. A diagnosis of this type would, however, have led to the classification of the case as one of primary bone tumour if it was accompanied by histological, radiological, or surgical evidence that the tumour arose from bone. If the diagnosis implied that the primary tumour involved two contiguous bones, the first named was regarded as the site of origin.

Tumours were classified as being of a specific histological type only when there was definite histological evidence to this effect. A hospital diagnosis of "osteogenic sarcoma of femur" was not regarded as sufficient to justify classifying the tumour as of this particular histological type, unless a histological report which substantiated the diagnosis was also given; in the absence of such a report, the tumour was classified as a primary tumour of bone of unspecified histological type. Reticulum-cell sarcomas were classified as bone tumours only if there was positive evidence that the tumour was regarded as arising from bone. Myelomatosis was not regarded as a bone tumour; but myeloma (with or without reference to plasma cells) was, if it appeared to have been a solitary lesion. Adamantinomas of the jaw arise from the epithelial covering of the teeth and were not classified as bone tumours; the one adamantinoma of the tibia was regarded as a bone tumour, although the origin of this type of tumour is obscure.

When further information was obtained the data on the death certificate were not used in reaching the final diagnosis unless: (1) the hospital data clearly indicated a primary bone tumour but did not specify the bone of origin; or (2) Paget's disease was mentioned on the certificate but was not mentioned by the hospital. In these circumstances the information on the certificate was used to determine the bone of origin or to classify the case as one associated with Paget's disease.

When additional information was obtained the data were used to compare the certified diagnosis with the final diagnosis. This comparison enabled an estimate to be made of the reliability of the certified cause of death,

subdivided according to the place of death, age and sex of the patient, the affected bone, and the histological description of the tumour given by the certifying doctor. On this basis it was possible to estimate the number of cases of true primary bone tumour likely to have been included among the cases for which no further information had been obtained. An estimate of the total mortality from primary bone tumours could then be made by summing the cases for which the diagnosis was confirmed, and an estimated number of true bone-tumour cases corresponding to those in which the only information was that provided by the death certificates. The validity of this procedure is discussed below.

Results

Altogether, 1,180 deaths were attributed to primary tumours of the bone in persons under 65 years during the three years of the investigation (Registrar-General, 1953, 1954, 1955). Of these, 11 were excluded because the death related to a foreign national (five cases) or because the cause of death had obviously been wrongly assigned (six cases). Additional information was obtained for 990 of the remaining 1,169, leaving 179 (15.3%) in which the only information available was that given on the death certificate. Among the 990 cases in which further information was obtained there were 516 (52.1%) in which the correct diagnosis was thought to have been a primary bone tumour. In a further 25 cases (2.5%) the possibility that there was a primary bone tumour was not excluded and the diagnosis was regarded as uncertain. In the remainder (45.4%) no primary bone tumour was thought to have been present. Histological evidence of the nature of the tumour was available in 77% of the cases in which the diagnosis of a primary bone tumour was accepted. The distribution of the various histological types is shown in Table I.

TABLE I.—*Number of Tumours of Each Histological Type Accepted as Primary Tumours of Bone*

Type of Tumour	No. of Cases
Osteosarcoma	144
Chondrosarcoma	66
Spindle-cell sarcoma	27
Fibrosarcoma	24
Ewing's tumour of bone	19
Giant-cell tumour	13
Reticulosarcoma	13
Chordoma	12
Round-cell sarcoma	8
Various (myeloma 2, angiosarcoma 2, myxosarcoma 2, adamantinoma 1, leiomyosarcoma 1, liposarcoma 1, myxochondrosarcoma 1, myxofibrosarcoma 1)	11
Undifferentiated	14
Sarcoma, unspecified or "mixed cell"	44
Total with histological evidence	395
No histological evidence	121
Total accepted tumours	516

Accuracy of Diagnosis

The accuracy of the diagnosis was not the same in all the subgroups examined. Among the 443 patients who died in hospital the diagnosis was confirmed in 253 (57%), whereas it was confirmed in 263 (48%) of the 547 patients who died elsewhere. A similar difference

TABLE II.—*Number and Percentage of Cases in which the Certified Diagnosis of a Primary Bone Tumour was Confirmed, Divided by Sex and Age*

Sex	Final Diagnosis	Age in Years													All Ages
		0–	5–	10–	15–	20–	25–	30–	35–	40–	45–	50–	55–	60–64	
Male	Primary bone tumour	4	7	25	53	28	20	13	11	17	21	35	37	47	313
	Other diagnosis*	5	5	4	9	7	8	8	15	20	27	40	54	60	262
	Per cent. primary bone tumour	44%	78%		84%		73%		44%		46%		42%		55%
Female	Primary bone tumour	2	10	14	28	23	9	13	10	13	12	20	15	29	198
	Other diagnosis*	4	3	5	4	5	10	9	7	11	20	34	44	56	212
	Per cent. primary bone tumour	33%	75%		84%		55%		56%		37%		31%		48%
Male and female	All diagnoses	15	25	48	94	63	47	43	43	61	80	129	150	192	990
	Per cent. primary bone tumour	40%	68%	81%	86%	81%	62%	60%	49%	49%	41%	43%	35%	40%	52%

* Cases in which it was uncertain whether a primary bone tumour was present are included here under "other diagnosis"; they are listed in the Appendix.

TABLE III.—*Number and Percentage of Cases in which the Certified Diagnosis of a Primary Bone Tumour was Confirmed, Divided by the Bone of Origin and the Pathological Description of the Tumour*

Certified Bones of Origin	Reference to Paget's Disease on Death Certificate:			No Reference to Paget's Disease on Death Certificate									All Cases Certified as Malignant Bone Tumour	
				Certified Specific Histological Type of Sarcoma:			Certified as Sarcoma Unspecified:			Certified as Carcinoma, Cancer, etc.:				
	No. with Final Diagnosis		Per cent. Primary Bone Tumour	No. with Final Diagnosis		Per cent. Primary Bone Tumour	No. with Final Diagnosis		Percent. Primary Bone Tumour	No. with Final Diagnosis		Per cent. Primary Bone Tumour	All Diagnoses	Per cent. Primary Bone Tumour
	Primary Bone Tumour	Other Diagnosis		Primary Bone Tumour	Other Diagnosis*		Primary Bone Tumour	Other Diagnosis*		Primary Bone Tumour	Other Diagnosis*			
Upper limb	2	0	100%	14	1	93%	28	14	67%	0	5	0%	64	69%
Lower ,,	21	0	100%	81	11	88%	134	50	73%	5	9	36%	311	77%
Jaw (upper and lower)	1	0	100%	6	3	67%	16	22	42%	2	96	2%	146	17%
Ethmoid	0	0	—	0	0	—	0	3	0%	0	29	0%	32	0%
Rest of skull	2	0	100%	4	3	57%	6	8	43%	0	18	0%	41	29%
Vertebrae or spine unspecified	1	0	100%	12	2	86%	4	17	19%	2	70	3%	108	18%
Sacrum	0	0	—	15	1	88%	7	8	47%	2	8	20%	41	59%
Shoulder girdle†	0	0	—	4	1	80%	12	12	50%	1	2	33%	32	53%
Ribs or sternum	0	0	—	16	1	94%	16	11	59%	0	13	0%	57	56%
Pelvis‡	6	0	100%	30	7	81%	29	21	58%	1	11	8%	105	63%
Multiple or unspecified	11	1	83%	23	3	88%	2	4	33%	0	9	0%	53	68%
All bones	44	1	98%	205	33	86%	254	170	60%	13	270	4%	990	52%

* See footnote to Table II. † Including shoulder unspecified. ‡ Including hip unspecified.

was recorded between men (55% confirmed tumours) and women (48% confirmed). Other factors, however, were found to affect the reliability of the diagnosis to a greater extent. Table II shows an analysis of the results according to the sex and age of the patient, and it is seen that the reliability varied from 86% at ages 15–19 years to about 40% at ages 45 to 64 years. Still greater differences were recorded when the data were analysed according to the anatomical site of the tumour and the pathological description given by the doctor who signed the death certificate (Table III). The reliability varied from 77% when the primary was said to have arisen from bones of the lower limb to 0% when the origin was in the ethmoid, and from 98% when Paget's disease of bone was said to have been associated with the tumour to 4% when the presence of Paget's disease was not referred to and the growth was described as carcinoma or by some non-specific term such as cancer, malignant neoplasm, or malignant new growth.

In view of the large differences in the various anatomical and pathological groups, the possibility has to be considered that the smaller differences observed in the other groups may result from differences in the distribution of the place of death and the sex and age of the patient in the anatomical and pathological groups. A calculation has therefore been made of the significance of each of the five variables examined when the effect of the other four factors is taken into account. First the number of age and anatomical groups shown in Tables II and III was reduced by combining groups in which the proportions of confirmed diagnoses were similar. Tables were then prepared showing the proportion of confirmed diagnosis in 480 subgroups defined by place of death (hospital or elsewhere), sex, age (0–9 years, 10–24 years, 25–34 years, 35–44 years, and 45 years and over), anatomical site (limbs, jaws, ethmoid, rest of skull, spine excluding sacrum, and other and unspecified sites), and pathological description (Paget's disease present and, in the absence of Paget's disease, specified type of sarcoma, unspecified sarcoma and other descriptions). The expected number of confirmed cases could then be calculated separately for each characteristic independently of variation of the others.

For example, there were 31 cases described as sarcoma of a limb bone, without specification of the histological type and without reference to Paget's disease, in men aged between 10 and 24 years who died at home; and there were 20 similar cases in women. Altogether the diagnosis was confirmed in 47 cases, so that the expected numbers of confirmed cases in men and in women, if there was no difference in the reliability of the diagnosis in the two sexes, would be $31 \times 47/51$ (i.e., 28.57) and $20 \times 47/51$ (i.e., 18.43). The numbers actually observed were 29 and 18. Similar calculations were made for each of the other subgroups, and the final comparison was made by summing all the expected numbers separately for each sex and comparing the totals with the observed numbers of confirmed cases in men and in women.

The results are shown in Table IV. They show clearly that one factor is of much greater importance than all the others in determining the reliability of the certified diagnosis of a primary bone tumour—and that is the certifying doctor's pathological description of the disease.

Evidently the diagnoses are intrinsically more reliable than would appear on first examination of the crude mortality data. The responsibility for the low proportion of cases in which the diagnosis of a primary bone tumour is confirmed lies not so much with the certifying doctor as with the international rules, which result in classifying "carcinoma of the jaw," "carcinoma of the ethmoid," and "cancer of the vertebra" as primary bone tumours. As might have been anticipated, the first two diagnoses are used to describe carcinomas of the mucous membrane covering the jaw bones and lining the ethmoid sinus, and the third corresponds to a diagnosis of bony metastases from a carcinoma elsewhere in the body. When there is evidence to show that the neoplasm actually originated in bone, the certifying doctor usually describes it as a bone sarcoma and he often adds its exact histological description.

TABLE IV.—*Number of Confirmed Cases of Primary Bone Tumour Divided Separately by Place of Death, Sex and Age of Patient, Affected Bone, and Pathological Description on the Death Certificate, Compared with the Number Expected After Allowing for the Effect of the Other Four Characteristics*

Characteristic	No. of Cases Observed	No. of Cases Expected	Observed Cases as Percentage of Expected	χ^2	n	P
Place of death:						
Hospital	251	244·6	102·6	0·318	1	0·5<P<0·7
Elsewhere	265	271·4	97·6			
Sex:						
Male	318	311·7	102·0	0·322	1	0·5<P<0·7
Female	198	204·3	96·9			
Age:						
0–9 years	23	24·3	94·7	5·899	4	0·2<P<0·3
10–24 ,,	171	147·5	115·9			
25–34 ,,	55	57·6	95·5			
35–44 ,,	51	54·5	93·6			
45–64 ,,	216	232·1	93·1			
Bone:						
Limb bone	285	261·0	109·2	11·075	5	P=0·05
Ethmoid	0	3·0	0·0			
Jaw	25	31·0	80·6			
Rest of skull	12	15·3	78·4			
Vertebrae excluding sacrum	18	28·7	62·8			
Other bones and multiple and unspecified sites	176	177·0	99·4			
Pathological description:						
Paget's disease present	44	27·6	159·4	54·318	3	P<0·001
Paget's disease not referred to:						
Specified type of sarcoma	205	166·0	123·5			
Sarcoma unspecified	254	264·3	96·1			
Other descriptions	13	58·1	22·4			

In present circumstances, however, it would be unwise to ignore all the other factors completely. After the effect of the pathological description is taken into account there still appears to be some variation in the reliability of the diagnosis applied to different bones. No cases of primary tumour of the ethmoid were confirmed, even though a few were described as sarcomas, and the reliability of the diagnosis of sarcoma of the vertebra was less than that of sarcoma of the femur. There is no reason to suppose that there is any great variation between most of the bones; but, on the present evidence, it seems reasonable to distinguish five groups within which the diagnoses may be regarded as equally reliable. These are, in order of reliability of the diagnosis, (1) limb bones; (2) sacrum, pelvis, shoulder-girdle, ribs, and sternum; (3) skull, including jaw but excluding ethmoid; (4) spine, excluding sacrum; and (5) ethmoid. Cases in which the site of the bone is not stated or more than one bone is specified have been classed in group 2.

After allowance is made for anatomical site and pathological description there is little difference in the reliability of the diagnosis in different age-groups. The

differences are not statistically significant, but until more evidence is obtained it seems better to assume that there is some difference between age-group 10–24 years and the others. If these three factors are taken into account the differences between the reliability of the diagnosis in men and in women, and between patients who die in hospital and elsewhere, can be ignored.

Estimate of Mortality Rates

The 990 cases in which further information was obtained about the cause of death have therefore been classified in four pathological groups and subdivided in five bone and two age subgroups. The total numbers of cases in each subgroup and the numbers in which the diagnosis was confirmed are shown in Table V.

From these data it is possible to estimate the number of true primary bone tumours which corresponded to the 179 certified causes of death for which no further information was obtained. For example, a death attributed to "sarcoma of the pelvis" in a man aged 55 years may be estimated as having 54 chances in 103 of being due to a primary bone tumour, and the death can be regarded as contributing, on average, 0.52 (54/103) of a case in the particular sex and age group. The validity of this estimate depends partly on the number of cases for which information had been obtained and partly on the degree of similarity between those for which information was obtained and those for which it was not. A comparison between the two groups is shown in Table VI. It is understandable that it was more difficult to obtain information from a general practitioner than from a hospital and more deaths occurred outside hospital among the group without further information than among those with. This difference is presumably reflected in the higher proportion of deaths in the oldest age-group and in the greater proportion of deaths attributed to malignancy of the spine and in the greater proportion not specified as sarcoma. All these factors can, however, be taken into account by using the proportion appropriate to each case, which is shown in Table V. The proportions are, at best, only approximations; the accuracy of the diagnosis in the unknown group may have been affected by other factors that have not been taken into consideration—for example, the age of the certifying doctor and the place of residence—but in the absence of more accurate information it seems reasonable to use these proportions to provide the best available estimate. On this basis, the number of primary bone tumours corresponding to the group of 179 certified deaths without further information is 81.4. The reliability of the diagnosis in this group as a whole (45%) is, as would be expected from inspection of Table VI, somewhat lower than the reliability in the main group for which further information was obtained (52%).

If the 81 presumed cases are added to the 516 confirmed cases of primary bone tumour, an estimate is obtained of the total mortality from primary bone tumours in England and Wales in 1951–3. Age-and-sex specific death-rates calculated in this way for 11 bones or groups of bones are shown in Tables VII and VIII. These rates are minimum rates, since 25 cases (listed in the Appendix) in which the diagnosis was uncertain have been regarded as not being primary bone tumours and no allowance has been made for the misdiagnosis of primary bone tumours under some other rubric.

An estimate of the maximum effect of the first factor can be made by assuming that in all 25 cases a primary bone tumour was, in fact, the cause of death. If this is done, the proportions shown in Table V are slightly altered and the estimated number of true bone tumours corresponding to the 179 cases in which no further information was obtained is increased to 47%. The effect on the estimates of the total mortality rates is small; the estimate of the annual male mortality rate at all ages under 65 years is increased from 62.9 to 65.3 per 10,000,000 men and of the female mortality rate from 38.9 to 41.6 per 10,000,000 women.

On present information it is impossible to make any quantitative estimate of the number of primary bone

TABLE VI.—*Comparison Between Cases With and Without Information Additional to the Certified Cause of Death*

Characteristics	Cases with Further Information		Cases without Further Information	
	No.	Per cent.	No.	Per cent.
Place of death:				
Hospital	443	45	29	16
Elsewhere	547	55	150	84
Sex:				
Male	580	59	96	54
Female	410	41	83	46
Age:				
0–9 years	40	4	6	3
10–24 ,,	205	21	24	13
25–44 ,,	194	20	35	20
45–64 ,,	551	56	114	64
Bone:				
Limb bone	375	38	64	36
Ethmoid	32	3	4	2
Rest of skull	187	19	32	18
Vertebrae, excluding sacrum	108	11	35	20
Other bones and multiple and unspecified sites	288	29	44	25
Pathological description:				
Paget's disease present	45	5	6	3
,, ,, not referred to:				
Specified type of sarcoma	238	24	33	18
Sarcoma unspecified	424	43	74	41
Other descriptions	283	29	66	37

TABLE V.—*Number of Cases Certified as Bone Tumours and Number of Confirmed Cases, Divided by Pathological Description, Affected Bone, and Age of Patient*

Paget's Disease	Histological Description of Tumour	Age of Patient (in Years)	Number of Deaths Attributed to Tumours of									
			Limb Bones		Other and Unspecified Bones		Skull, Excluding Ethmoid		Vertebrae, Excluding Sacrum		Ethmoid	
			Confirmed	Total	Confirmed	Total	Confirmed	Total	Confirmed	Total	Confirmed	Total
Present	All descriptions	25–64	23	23	17	18	3	3	1	1	—	—
Absent	Specified type of sarcoma	10–24	48	53	23	26	2	2	1	1	—	—
		Other ages	47	54	65	75	8	14	11	13	—	—
	Sarcoma unspecified	10–24	74	81	12	19	5	6	3	7	—	—
		Other ages	88	145	54	103	17	46	1	14	0	3
	Other descriptions	10–24	1	1	2	3	0	2	0	3	0	1
		Other ages	4	18	2	44	2	114	2	69	0	28

tumours which have not been diagnosed, or in which the cause of death has been certified in such a way that the death has been misclassified. Likely sources of error include the classification of a primary bone tumour as tumour of soft tissue, reticulosarcoma, metastatic neuroblastoma, or as giving rise to carcinomatosis of unknown origin. It seems unlikely, however, that a large proportion of cases will have been misdiagnosed, as (1) the common types of osteogenic sarcoma and chondrosarcoma arise in an accessible site, and (2) young people who develop a fatal illness are nearly always investigated in hospital.

TABLE VII.—*Male Mortality from Primary Tumours of the Bone in England and Wales, 1951–3*

Site of Primary Tumour	Annual Death Rate per 10,000,000 Males Aged (in Years):												
	0–	5–	10–	15–	20–	25–	30–	35–	40–	45–	50–	55–	60–64	0–64
Humerus	0·0	1·9	16·1	11·9	4·5	4·7		1·7		3·4		9·4		5·2
Radius or ulna	0·0	1·9	0·0	0·0	0·0	0·0		0·0		1·1		2·3		0·6
Femur	3·7	3·8	20·5	60·7	28·9	13·1		12·0		16·7		47·0		20·6
Tibia or fibula	0·0	0·0	18·4	43·0	17·9	4·5		1·0		4·8		4·9		8·0
Other limb bone	0·0	0·0	0·0	7·2	0·0	1·0		1·7		1·1		2·6		1·4
All limb bones	3·7	7·6	54·9	122·7	51·4	33·0	13·7	9·5	22·8	20·9	34·4	52·1	82·8	35·7
Mandible or maxilla	0·0	1·9	1·9	0·0	4·2	2·1		4·7		1·2		6·5		2·6
Rest of skull	0·0	0·0	0·0	2·4	0·0	1·0		0·0		1·2		5·5		1·1
Spine (including sacrum)	1·8	0·0	4·6	4·8	4·5	3·1		2·1		7·9		11·1		4·5
Ribs	0·0	1·9	0·0	2·4	6·8	2·1		4·0		7·2		18·9		5·0
Clavicle or scapula	0·0	1·0	0·0	0·0	4·5	2·1		1·0		7·8		9·7		3·2
Pelvis	1·8	1·9	2·3	5·0	2·3	3·1		4·2		17·0		39·2		9·1
Bones, other than in limbs	3·7	6·7	8·8	14·5	22·3	14·7	12·4	16·9	15·1	24·4	63·1	75·3	108·9	25·5
Bone, unspecified	1·6	0·0	0·0	0·0	0·0	1·0		2·1		2·8		5·6		1·7
All bones	9·0	14·4	63·7	137·2	73·6	47·8	28·2	26·4	41·9	50·5	97·5	134·7	195·3	62·9

TABLE VIII.—*Female Mortality from Primary Tumours of the Bone in England and Wales, 1951–3*

Site of Primary Tumour	Annual Death Rate per 10,000,000 Females Aged (in Years):													
	0–	5–	10–	15–	20–	25–	30–	35–	40–	45–	50–	55–	60–	0–64
Humerus	0·0	6·0	2·4	9·6	4·5	1·0		3·0		2·8		6·8		3·7
Radius or ulna	0·0	0·0	0·0	0·0	0·0	0·0		0·0		0·0		1·3		0·2
Femur	1·9	10·0	14·1	42·4	13·6	7·7		9·2		15·2		26·4		14·6
Tibia or fibula	0·0	0·0	16·3	7·3	13·4	0·0		1·1		5·5		8·1		4·7
Other limb bone	0·0	0·0	0·0	0·0	0·0	1·0		1·0		0·0		1·3		0·5
All limb bones	1·9	16·0	32·8	59·3	31·6	8·9	10·7	12·3	16·1	13·5	34·2	30·9	58·2	23·6
Mandible or maxilla	2·5	2·0	2·4	2·4	4·5	3·7		1·0		3·3		2·8		2·7
Rest of skull	0·0	0·0	0·0	0·0	4·5	1·0		0·6		2·1		3·9		1·4
Spine (including sacrum)	2·9	0·0	2·4	4·8	4·5	5·0		3·9		2·2		3·0		3·3
Ribs	0·0	0·0	2·4	2·4	0·0	2·1		2·0		3·2		0·0		1·5
Clavicle or scapula	0·0	0·0	0·0	4·8	0·0	0·9		0·0		1·1		1·3		0·8
Pelvis	0·0	2·0	1·5	2·4	6·8	6·1		3·9		3·3		11·3		4·6
Bones, other than in limbs	5·5	4·0	8·7	16·8	20·4	18·0	19·6	9·1	13·7	14·5	15·8	12·1	33·5	14·3
Bone, unspecified	0·0	0·0	0·0	0·0	2·3	0·0		1·9		0·0		3·8		1·0
All bones	7·4	20·0	41·5	76·1	54·2	26·9	30·3	23·5	31·4	28·0	50·0	47·8	94·6	38·9

TABLE IX.—*Mortality from Primary Tumours of the Bone Asosciated with Paget's Disease, England and Wales, 1951–3*

Site of Primary Tumour	Annual Death Rate per 10,000,000*											
	Males Aged (in Years):							Females Aged (in Years):				
	35–	40–	45–	50–	55–	60–64	0–64	45–	50–	55–	60–64	0–64
Humerus	0·0		0·0		6·4		0·7	1·1		2·6		0·5
Femur	1·0		3·5		22·7		3·1	2·5		8·0		1·4
Tibia or fibula	0·0		1·1		3·5		0·5	0·0		1·3		0·2
Other limb bones	0·0		0·0		1·6		0·2	0·0		0·0		0·0
All limb bones	0·0	2·0	2·1	7·6	25·2	44·7	4·5	0·0	7·3	5·3	19·2	2·1
Mandible or maxilla	0·0		0·0		1·6		0·2	0·0		0·0		0·0
Rest of skull	0·0		0·0		3·2		0·3	0·0		2·6		0·3
Spine (including sacrum)	0·0		0·0		3·2		0·3	1·1		0·0		0·2
Clavicle or scapula	0·0		1·1		0·0		0·2	0·0		0·0		0·0
Pelvis	0·0		2·3		19·8		2·5	1·1		4·8		0·8
Bones, other than in limbs	0·0	0·0	0·0	7·3	21·7	34·9	3·5	0·0	4·4	0·0	15·5	1·3
Bone, unspecified	1·0		1·1		4·7		0·9	0·0		1·2		0·2
All bones	0·0	4·0	4·2	15·0	52·7	83·2	8·9	0·0	11·8	5·3	37·3	3·5

* No deaths were recorded among men under 40 years of age or among women under 50 years of age.

Paget's Disease of Bone

Estimates of the mortality from primary tumours of the bone associated with Paget's disease are given in Table IX. The figures may underestimate the true mortality, as specific inquiries about the presence of Paget's disease were not made and the available information is limited to that provided by the certified cause of death or by the data extracted from the hospital records. The deficiency is, however, unlikely to be great, as tumours associated with Paget's disease are more common in men and the mortality rates from tumours of the limb bones when Paget's disease was not reported were equal in both sexes at ages over 35 years.

No cases were reported with Paget's disease among men under 40 years of age or among women under 50 years of age. After 45 years of age the mortality increased rapidly, and by ages 60–64 years it accounted for over 40% of the total bone tumour mortality. The mean male mortality at ages 40–64 years was nearly three times the mean female mortality, and approximately the same ratio was observed for the two bones most often affected (femur and pelvis) and for all other bones taken together.

Age Distribution

Tables VII and VIII show that there is a peak in the mortality from tumours of the limb bones at ages 15–19 years in both sexes. This peak presumably reflects a peak in incidence several years earlier, and it is reasonable to relate it to the adolescent spurt in growth which is at a maximum at about age 13½ years in boys and 11¾ years in girls. At older ages the mortality falls to a minimum in adult life at ages 25–34 years in women and five years later in men; it then rises until at ages 60–64 years the mortality approaches the maximum recorded in late adolescence. This type of distribution is shown by all the principal tumours in the group—that is, by tumours of the humerus, femur, and tibia or fibula. The number of cases recorded for the other limb bones is too few to show whether or not they have a similar bimodal distribution. Examination of Table IX shows that the greater part of the rise in mortality in middle age is due to tumours associated with Paget's disease. The variation of mortality with age in the absence of Paget's disease is illustrated in Fig. 1. In middle age the mortality increases approximately in proportion with the age—a rate of increase which is slower than for any other of the principal types of malignant disease.

Tumours of bones other than the limb bones account for about 30% of the total mortality. Tables VII and VIII show that the mortality rises slowly from birth to ages 20–24 years and then remains fairly steady for the next 20 years. In both sexes, however, the mortality at ages 20–24 years is slightly higher than that at ages 25 to 44 years, and it is possible that the tumours in this group also show an "adolescent peak" in mortality similar to, but much less marked than, that recorded for tumours of the limb bones. If so, it may be noted that the peak in mortality occurs in the five-year period subsequent to that recorded for tumours of the limb bones and it is possible that this is related to the fact that the bones of the shoulder and pelvic girdles, the thorax, and the spine both begin and end their adolescent growth spurt about a year later than the long bones of the limbs (Tanner, 1961).

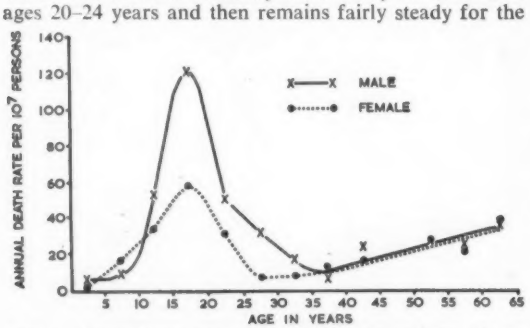

FIG. 1.—Annual death rate per 10,000,000 persons from primary tumours of the limb bones, excluding cases associated with Paget's disease of bone; by sex and five-year age-group up to age 65 years: England and Wales, 1951–3.

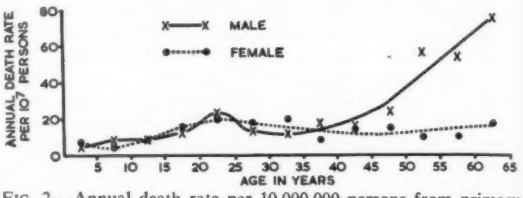

FIG. 2.—Annual death rate per 10,000,000 persons from primary tumours of bones, other than limb bones, excluding cases associated with Paget's disease of bone; by sex and five-year age-group up to age 65 years: England and Wales, 1951–3.

At older ages the mortality from tumours of bones other than limb bones rises sharply in men; but it remains constant in women until age 60–64 years, when there is a small increase. The variation of mortality with age in the absence of Paget's disease is illustrated in Fig. 2. The male mortality still rises sharply after age 45 years, but the female mortality now remains practically constant throughout.

Sex Ratio

The data in Tables VII and VIII show that the total mortality from bone tumours is 62% higher among men than among women. The difference is, however, not constant and varies sharply with age, the type of bone, and the presence or absence of Paget's disease. For tumours of the limb bones the male preponderance is greatest when the mortality is at a maximum—that is, 2.1 to 1 at ages 15–19 years—and disappears at ages 0–9 and 30–39 years, when the mortality is low. That this should be so may perhaps be explained by differences in the response of the limb bones to the adolescent growth spurt. At this period the long bones of the limbs increase in length in both sexes; but the increase in length and the relative increase in breadth are substantially greater in boys (Tanner, 1961). As a result it becomes possible in the majority of instances to distinguish a male femur from a female femur after puberty, whereas before puberty they are usually indistinguishable.

At ages 40 years and over the mortality from tumours of the limb bones again becomes higher in males. At this period, however, the excess can be attributed entirely to the occurrence of tumours in relation to Paget's disease. In the absence of Paget's disease the male and female death rates are practically identical (Fig. 1); at ages 30–64 years the mean annual death rates are respectively 22.1 per 10,000,000 men and 20.4 per 10,000,000 women.

For bones other than limb bones death rates are practically equal in both sexes up to the age of 45 years, the mean annual death rates being 12.8 per 10,000,000 men and 12.9 per 10,000,000 women. At older ages the male mortality rises above the female and by ages 60–64

years the ratio of the rates is more than 3 to 1. In this case the male preponderance becomes more marked in the absence of Paget's disease, and the ratio of the rates then rises to more than 4 to 1 (Fig. 2). Tables VII–IX show that the male preponderance is shared by all bones in this group other than the bones of the skull and jaw. The greatest contribution is, however, made by tumours of the ribs and shoulder-girdle. For the tumours, in the absence of Paget's disease, the mean annual death rate at ages 45 to 64 years was seven to eight times higher in men than in women; for tumours of the spine and pelvis it was four times higher.

Histological Type

The study was not intended to provide detailed data for the various pathological types of primary bone tumour, and no attempt was made to standardize the criteria for histological diagnosis. In these circumstances it is not justifiable to estimate the relative frequency of the different tumours. The age-and-sex distribution of cases described as (1) osteosarcoma and (2) chondrosarcoma is given in Fig. 3, which shows that the peak mortality in

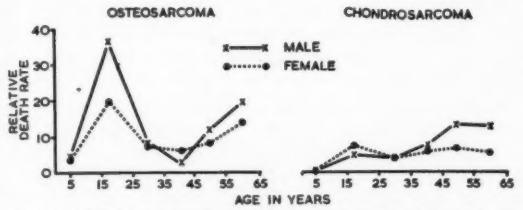

FIG. 3.—Relative mortality at different ages under 65 years from osteosarcoma and from chrondrosarcoma, by sex: England and Wales, 1951–3.

adolescence is principally due to osteosarcoma; but that there is also a small peak in the mortality from chondrosarcoma. The male excess in chondrosarcoma at ages 45 years and over is due to tumours of the ribs and shoulder-girdle and to a less extent to tumours of the pelvis. Many cases of osteosarcoma and chondrosarcoma must, however, have been omitted because of lack of sufficiently detailed histological information, and these figures cannot usefully be compared with those reported by Price (1955, 1958) from the Bristol Tumour Registry.

Geographical Distribution

Data for the sex-and-age distribution of the population obtained in the 1951 census allow an estimate to be made of the expected number of deaths in different parts of the country. Figures for each county or combination of counties have been compared with the estimated numbers of deaths occurring during the years 1951–3 and are reported elsewhere (Court Brown, Doll, Heasman, and Sissons, 1961). The results fail to provide conclusive evidence of any geographical variation in mortality, although they suggest that there may be a deficit in some parts of Southern England. Data are not, as yet, available to enable a direct comparison to be made between the level of bone-tumour mortality and the total radiation dose received in bone. For this purpose it would be necessary to have a measure of the radioactivity in bones from different parts of the country. A crude comparison between the estimated mortality from primary bone tumours and the radioactivity of the water supplies in 19 counties (Turner, Radley, and Mayneord, 1961) has failed to show any correlation (Court Brown *et al.*, 1961).

Summary

The mortality attributed to primary malignant tumours of bone in England and Wales in 1951–3 has been examined. These years were chosen because 1953 was the year in which the first megaton nuclear bomb was exploded and suitable data were not available for any years before 1951.

Records of deaths attributed to primary malignant tumours of bone in persons aged under 65 years were examined by the General Register Office and a questionary was sent to the doctor who signed the death certificate or to the hospital in which the patient had been treated.

Evidence about the nature of the diagnosis was obtained for 990 cases out of a total of 1,169—that is, for 84.7%. In 516 cases (52.1%) the diagnosis of a primary bone tumour was confirmed; in 449 (45.4%) the diagnosis was thought to be not a primary bone tumour, and in 25 (2.5%) the diagnosis was uncertain.

The diagnosis was found to be more reliable: (1) for deaths occurring in hospital (57% confirmed) than for deaths occurring elsewhere (48%); (2) for men (55% confirmed) than for women (48%); (3) for deaths at ages 15–19 years (86% confirmed) than for other ages (40% at ages 45 to 64 years); (4) for deaths attributed to primary tumours of a bone in the lower limb (77% confirmed) than for primary tumours of other bones; and (5) for deaths in which Paget's disease was said to be associated with the tumour (98% confirmed) or, in the absence of Paget's disease, for deaths in which the tumour was specified as being a particular histological type of sarcoma (86%) than for carcinoma or cancer of bone (4%).

The pathological description of the tumour given by the certifying doctor was the most important factor. After it had been allowed for there was still some difference between the reliability of the diagnosis for different bones and, possibly, for deaths occurring at ages 10–24 years and at other ages.

The additional information obtained for 990 deaths allowed an estimate to be made of the proportion of the remaining deaths which were properly attributable to primary tumours of bone. It could then be estimated that 597 deaths from primary bone tumours occurred among persons aged under 65 years in England and Wales during the three years 1951–3. The minimum annual mortality was estimated to be 6.3 per 1,000,000 men and 3.9 per 1,000,000 women. The true figures must be somewhat higher, as some of the 25 deaths in which the diagnosis was uncertain were probably due to bone tumours and some deaths will have been misclassified under other rubrics.

Examination of the sex and age-specific mortality rates attributed to different bones shows that:

(1) The maximum mortality from tumours of the limb bones is recorded in both sexes at ages 15–19 years; at this age the ratio of the male and female rates is also at a maximum (2.1 to 1).

(2) The mortality from these tumours falls from age 20 to 34 years and rises again from age 40 years.

(3) The increase at ages over 40 years is largely due to tumours associated with Paget's disease; the mortality from tumours of the limb bones not associated with Paget's disease increases slowly between ages 35 and 64 years and is equal in both sexes.

(4) The mortality from tumours of bones other than limb bones shows only a faint peak at ages 20–24 years.

(5) At ages under 45 years the mortality is approximately equal in both sexes.

(6) At ages 45 years and over there is a sharp increase in the mortality among men but very little increase among women. In the absence of Paget's disease the discrepancy is more marked and among women the mortality remains practically constant. The male excess in this group is due principally to tumours of the ribs and shoulder-girdle.

No significant difference in the geographical distribution of bone-tumour mortality has been demonstrated.

We are grateful for the helpful advice of Dr. R. Acheson, Dr. J. H. Marshall, and Dr. J. M. Tanner.

APPENDIX

In 25 cases it was impossible to decide whether a primary bone tumour was present. There was no reference to Paget's disease on any of the death certificates. The descriptions of these cases given on the death certificates were:

Case No.	Sex	Age (Yrs.)	Affected Bone	Histological Description	Place of Death
1	M	3	Maxilla	Osteosarcoma	Home
2	M	6	Jaw	Sarcoma	Hospital
3	M	8	Spine	,,	Home
4	M	18	Calcis	Ewing's tumour	,,
5	M	37	Ilium	Sarcoma	Hospital
6	M	45	Femur	,,	Home
7	M	46	Ribs	,,	Hospital
8	M	50	Pelvis	Osteosarcoma	Home
9	M	56	Skull	Sarcoma	,,
10	M	59	Femur	,,	,,
11	M	59	Humerus	Malignant neoplasm	,,
12	F	9	Lumbar spine	Tumour	,,
13	F	23	Fibula	Ewing's sarcoma	,,
14	F	26	Ribs	Sarcoma	,,
15	F	33	Rib	,,	Hospital
16	F	48	Ilium	,,	Home
17	F	50	Pelvis	Osteosarcoma	,,
18	F	50	—	Chordoma	Hospital
19	F	57	Vertebrae	Sarcoma	,,
20	F	60	Ethmoid	,,	Home
21	F	60	Rib	,,	,,
22	F	61	Femur	,,	Hospital
23	F	63	Orbit	,,	Home
24	F	63	Lumbar spine	Carcinoma	,,
25	F	64	Pelvis	Sarcoma	Hospital

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PLEA FOR GREATER USE OF CYTOLOGICAL STUDIES IN EARLY DETECTION OF CANCER

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Among the most important factors influencing the prognosis of malignant disease are the extent of the growth and the degree of its spread. By the time a tumour gives rise to symptoms it may have reached proportions which render treatment difficult and the prognosis poor. The examination of body fluids by the cytological method makes possible the discovery of malignant disease when the tumour is still of microscopic proportions, and thus detection at such an early stage can help to improve prognosis. Furthermore, the method is also of considerable assistance in helping to differentiate malignant disease from other pathological conditions, particularly where other diagnostic tests may be inconclusive.

The cytological method originated in England over 100 years ago, when Walshe (1851) observed fragments of malignant tissue in sputum. From that time onwards other workers, both in this country and elsewhere, carried out much work in this field, and in 1927 Dudgeon and Patrick, experimenting with the wet-fixation technique at St. Thomas's Hospital, examined sputum, urine, and other body secretions for the presence of malignant cells. At about the same time in the United States of America, Papanicolaou (1928) used a similar technique for diagnosing cancer of the female genital tract, and by 1940, having realized the potentialities of the method, he devoted his time wholly to its development, so that to-day, after many years of extensive trial all over the world, it has become inevitably associated with his name and now is used as an everyday routine for cancer detection in most hospitals in the Americas and on the Continent. In Great Britain much excellent cytological work has also been done in a number of centres for some years, but, as Saxton (1960) points out, this country lags far behind both the U.S.S.R. and the U.S.A., where cytological examinations for cancer of the uterus have become routine procedures, and, although in a few localities schemes for this purpose are in operation, he pleads for the establishment of more such schemes in all centres of population where these examinations could be carried out regularly.

Principal Uses of the Cytological Method

Female Genital Tract.—Undoubtedly the most successful application of the cytological method has been its use for the detection of early invasive or pre-invasive carcinoma of the cervix uteri. In Great Britain, Anderson (1950), Wachtel and Plester (1952), Way (1953), McLaren (1953), and Egerton (1957), after trying out the method as a research project, found that their results were so encouraging that they now continue to use it as a routine test in the gynaecological clinics of the hospitals where they work. Wrigley (1960) maintains that it is essential as an additional means of investigation where there is the slightest sign or suspicion

of malignant disease. He also states that it should be used as a routine procedure when changing a ring pessary and for following up treatment for cervical carcinoma. The method is much less reliable for diagnosing carcinoma of the body of the uterus; nevertheless, Wachtel and Plester (1952) were able to detect not only five cases of unsuspected endometrial carcinomata among 2,000 patients examined but also four unsuspected ovarian adenocarcinomata. Moore (1958) at the Royal Society of Medicine demonstrated a case from the Royal Free Hospital in which an unsuspected carcinoma in a Fallopian tube was discovered by this means.

Urinary Tract.—Cytology is now used as an essential method in the control of bladder tumours of occupational origin, such as those occurring among workers in the dyestuffs and rubber industries (Crabbe, Cresdee, Scott, and Williams, 1956). Since its introduction as a diagnostic measure for this purpose it has already helped to prolong the lives of most of the men who have been affected. Between the years 1951 and 1956 some 1,800 men had their urine examined routinely by the method and 62 new cases of bladder tumours were discovered. Although similar work has been carried out in America, Germany, and Italy for some years no results had been published from these countries until last year, when Melamed, Koss, Ricci, and Whitmore (1960) in America reported on some observations on bladder tumours developing in workers exposed to para-aminodiphenyl, a powerful bladder carcinogen. Apart from diagnosing occupational bladder tumours the examination of urine may be of help in hospital routine in detecting bladder growths where cystoscopy is contraindicated or refused and in locating or confirming the diagnosis of tumours in the renal pelves or ureters. It is of little or no use for detecting tumours of the renal parenchyma.

A further application in the genito-urinary field is for the detection of carcinoma of the prostate by the examination of fluid obtained by massage, and Fergusson and Gibson (1956) found that the method was reliable for indicating prostatic malignancy as it gave results comparable with those of biopsy without the attendant risk from trauma, haemorrhage, and infection. They found that it could be safely repeated many times and that it affords a useful method for indicating response or otherwise to hormonal therapy.

Respiratory System.—With the increase in the incidence of lung cancer during the last few decades the examination of sputum and bronchial washings for the presence of malignant cells is a most valuable addition to current methods for helping to detect these growths. Sometimes it is the only means of detecting the disease at a stage early enough for successful treatment to be instituted or of confirming a clinical diagnosis when *x*-ray examination is equivocal and bronchoscopy negative. Some of the earliest systematic cytological investigations on sputum were performed by British pathologists (Dudgeon and Patrick, 1927; Gloyne, 1937; Schuster, 1943; Bamforth, 1946).

Pleural and Ascitic Fluids.—The cytological examination of serous effusions can be of great diagnostic and prognostic significance, as the occurrence of ascites or a pleural effusion in malignant disease is a grave and often terminal phenomenon. The results of the examination can be of great help not only in making a differential diagnosis but sometimes as a guide to the effectiveness of treatment.

Alimentary Tract.—Washings from the stomach are also examined for malignant cells, and Schade (1958), using a simple lavage technique, states that small malignant lesions, often confined to the mucosa, were easier to detect than the larger advanced tumours. Burnett, MacFarlane, Scott Park, and Kay (1960), also using a similar technique, found that cytology was a useful adjunct to other routine methods of diagnosis for gastric carcinoma, but owing to the high incidence of false-negative results (38%) cytology was unreliable as a screening test. Oakland (1957) uses the method for the examination of washings from the colon and rectum, and he found that it was most successful in the diagnosis of carcinoma of the descending and sigmoid colons.

Technique

The making and staining of the smears is so simple that it can be done in any small histological laboratory. The actual details of technique vary in different cytological schools. Pathologists tend to prefer fixation of the smear while it is still wet and to stain with haematoxylin and eosin (Bamforth, 1946; Philps, 1954), while the haematologists prefer drying and fixation followed by one of the Romanowsky stains (Spriggs, 1957). On the other hand, the followers of Papanicolaou and those engaged in endocrine work favour wet fixation and the use of the polychrome stains of Papanicolaou (1954) or Shorr (1940).

All of these techniques are simple, but it really does not matter which method is used, it is purely a question of preference. The best method is that with which the cytologist is most familiar. The most popular is probably that of Papanicolaou, and in his *Atlas* he describes fully the different ways of obtaining the materials, making the smears, and how to stain them by his method. Finally, for the proper examination of the smears the equipment must include a good binocular microscope with a mechanical stage and a reasonably powerful and accurate source of illumination for dry high-power work. The reading of the slides is greatly facilitated if $\times 10$ or $\times 15$ wide-field eyepieces are used. The interpretation of the smears and the criteria of malignancy have been described many times over in the copious literature on the subject, and these points again are fully discussed by Papanicolaou in his *Atlas*.

Use of the Cytological Technique at the Royal Free Hospital

The encouraging results of the cytological research work of Egerton (1957) in the gynaecological department of the Royal Free Hospital since 1952 have led to the adoption of the technique as a routine cancer detection test which is now applied to all women aged 30 and over attending the clinics. The method is also used in the department as an indication of ovarian function in the endocrine disorders of women (Egerton, 1957).

Although the cytological study of other body secretions, notably sputum (Findlayson, 1956) and serous effusions, has been done in the hospital for some years it was not until 1958 that a department was set up devoted entirely to the cytological examination of all types of materials.

The specimens examined include gastric washings as a screening test for carcinoma, but so far the experience here has been similar to that of Burnett *et al.* (1960) in that the incidence of false-negative results is too high

for the method to be reliable for this purpose. The accompanying Table is a summary of the results from May, 1958, to December, 1960.

Summary of Results

Specimens	No. of Patients	Tumours Found	Positive Smears	Confirmed	False Positives	False Negatives	Not Confirmed
Gynaecological	3,000	60	60 (100%)	48 (80%)	11 (18·3%)	12 (20%)	1
Respiratory ..	275	46	32 (69·6%)	30 (65·2%)	1 (2·03%)	16 (34·8%)	1
Serous effusions	147	57	51 (89·5%)	46 (80·7%)	0	11 (19·3%)	5
Urine	40	9	8 (88·9%)	6 (66·7%)	1 (11·1%)	3 (33·3%)	1
Gastric washings	228	15	6 (40%)	5 (33·3%)	0	10 (66·7%)	1

Of the gynaecological cases 16 (26·7%) were unsuspected.

Female Genital Tract

Since May, 1958, 3,000 cases have been examined; 48 tumours have been found by means of the cytological technique (39 cases of carcinoma of the cervix, 8 of carcinoma of the fundus, and 1 case of carcinoma of the ovary). Of these 48 cases, 16 had no signs or symptoms suggestive of carcinoma and were entirely unsuspected. Five proved on biopsy to be carcinoma *in situ*, eight proved to be early invasive carcinoma, and three proved to be adenocarcinoma of the body of the uterus. The remaining 32 cases were all clinically suspected. In four of these 32 cases it was possible to confirm the clinical suspicion by immediate staining and reading the smears before the patients left the department. In 11 cases the smears were not confirmed by biopsy, while one remains to be confirmed. Twelve cases showed no malignant cells in the smears and all of them proved to be carcinomas of the body of the uterus.

Example, Case 1.—The patient had been attending the gynaecological clinic since September, 1959, for treatment of a persistent vaginal discharge due to trichomonal infection. In November, 1959, smears were taken from the cervix and posterior fornix purely as a routine, as she had become 30 years of age during the course of her treatment. Malignant cells were seen in the smears and biopsy confirmed the presence of an early invasive carcinoma of the cervix. Irradiation therapy was followed by total hysterectomy. At the time of writing she was alive and well and was attending the gynaecological clinic for follow-up smears.

Respiratory Tract

Since May, 1958, 275 cases have been examined; 32 of these had malignant cells in the sputum, and 30 of them were proved to have carcinoma of the lung or bronchus. In one case no carcinoma was found at necropsy while the remaining case has yet to be confirmed. In 16 cases with proved carcinoma of the respiratory tract no malignant cells were found in the sputum.

Example, Case 2.—In January, 1960, a man aged 46 had a fit of coughing which was followed by a severe pain in the front of the chest that lasted for two or three days. This cleared up but recurred more severely in July, but this time it lasted longer and much brown sputum was produced. In September he was admitted to hospital, where it was noted that he had night sweats and was losing weight. An *x*-ray examination on September 8 showed a large opacity with cavitation in the left upper lobe which might have been due to a breaking-down growth, an abscess, or aspergillus infection. Smears of the sputum taken at this time contained malignant cells suggestive of a squamous-cell carcinoma. A week later bronchoscopy showed a stricture of the left upper lobe bronchus probably due to neoplasm. The biopsy section taken at the same time confirmed the presence of a squamous-cell carcinoma. He was discharged from hospital at the end of September after a lobectomy and is alive and well.

Pleural and Ascitic Fluids

Smears of 147 cases have been examined and 51 of these had malignant cells. In three of these cases the cytological reports were the first indication that the condition was due to malignant disease, and in two other cases the report was of great help in confirming the presence of a suspected neoplasm. However, in 11 cases where a tumour was found to be present no definitely malignant cells were seen. Five cases remain to be confirmed.

Example, Case 3.—A man aged 60 was admitted to hospital in December, 1959, complaining of abdominal discomfort and distension for four days. A tentative diagnosis of cirrhosis of the liver was made, but the ascitic fluid was found to contain many clusters of malignant cells. *X*-ray and barium-meal examinations were suggestive of oesophageal varices, but gastric carcinoma could not be completely excluded. His condition rapidly deteriorated and he died in January, 1960. Necropsy disclosed cirrhosis of the liver together with a carcinoma of the head of the pancreas, but there was no carcinoma of the stomach. The smears were the only tests to give a definite indication that malignant disease was present.

Urinary Tract

Only 40 specimens of urine have been examined since May, 1958. Eight of these cases had positive smears; six were proved to have tumours on further investigation, while in one case no tumour was found on cystoscopy and one case has yet to be confirmed. Three specimens sent from patients, later proved to have hypernephromata, contained no malignant cells. The usefulness of the technique is illustrated in the following case report.

Example, Case 4.—This patient, aged 68, had a carcinoma of the cervix uteri which was treated successfully in 1938. She came to the hospital in January, 1959, after an attack of haematuria, and it was thought that she might have a recurrence of this tumour which was involving the bladder. On gynaecological examination there was no clinical evidence of a local recurrence, so a catheter specimen of urine was obtained for cytological examination. The smears of the urine sediment contained many clusters of malignant cells which were suggestive of a transitional-cell carcinoma. On cystoscopic examination a bladder tumour was found which, on sectioning, proved to be a transitional-cell carcinoma. A partial cystectomy was performed in February, 1959, and the patient is alive and well.

Gastric Washings

Of 288 cases examined, 15 were suspected of having carcinoma of the stomach. Of these 15, only 6 showed malignant cells in the smears. Five were confirmed at operation, while one remains to be confirmed. Ten cases proved by other means of investigation to have gastric carcinoma showed no malignant cells in smears of the gastric washings.

Example, Case 5.—The patient, aged 44, was admitted to hospital in May, 1960, complaining of severe epigastric pain, which was relieved by vomiting and which had persisted for the last five years. *X*-ray examinations were inconclusive, but the smears of the gastric washings contained clusters of cells which were highly suspicious. Sections of gastric biopsy material showed the presence of gastric carcinoma, and this was confirmed by gastroscopy. A partial gastrectomy was performed in July, and sections of the stomach showed it to be a multifocal early gastric carcinoma. The patient was discharged from hospital in August and is alive and well.

Conclusions

In the comparatively few centres in this country where the cytological diagnosis of cancer has been practised for some years the successes have been such that the demand for its use has tended to increase. This is exemplified at the Royal Free Hospital, where during a brief period of some six years the successes of one or two research workers have resulted in the establishment of a department devoted exclusively to cytological cancer diagnosis with facilities for both teaching and research work. During this time the great advantages of the technique have become apparent. Firstly, and most important, as a routine procedure it can be used to detect tumours at a very early stage of development, often before signs and symptoms appear. It is simple to perform and need cause no alarm, inconvenience, or discomfort to the patient, and thus it can be repeated as often as may be necessary. The only inconvenience that a patient may be caused is in obtaining those materials where needles or other instruments have been used.

The chief disadvantages of the method are the time that is required to read the slides and the lack of trained personnel to do this. The taking and processing of the smears is simple, but the interpretation of the wide range of the cellular variations in the different types of body fluids requires considerable training. Until recently it was usually found necessary to go to America to gain the requisite experience, but now one or two cytological centres in London and the provinces provide facilities for teaching the technique and the interpretation of the smears. This should help to eliminate the necessity for sending personnel abroad for training, with the concomitant expense which that involves.

A plea is made for the more extended use of the method throughout the British Isles, where much of the original pioneer cytological work was done. The experience of cytological workers all over the world shows that the technique is well worth while, for if the detection of cancer when it is symptomless and at a very early stage of development is going to save or prolong lives—and there is reason to believe that it does—then the method is a most valuable weapon in the fight against cancer.

Summary

An account is given of the cytological technique for the early detection of malignancy which, though evolved in the early days to a great extent by British pathologists, was developed by Papanicolaou in America in such a way that it has practical application.

The principal and most successful uses of the method are described and reference is made to the processing, staining, and interpretation of the smears.

Although most of the published work on cytology comes from American and Continental laboratories, the references in this paper apply chiefly to publications from British cytologists.

A short account is given of the establishment of a cytology department and its use at the Royal Free Hospital during the last two years, with a record of the results obtained. Typical example cases are quoted. The advantages and disadvantages are discussed, and a plea is made for the more extended use in this country of this undoubtedly valuable weapon in the fight against cancer.

We thank Professor K. R. Hill for his encouragement and Miss Anne Robertson for carrying out the technical work and helping to read the slides. We are indebted to the British Empire Cancer Campaign for the generous help with a grant from which technical and laboratory assistance has been provided, thus enabling this work to be carried out.

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THYROGLOBULIN ANTIBODIES IN 1,297 PATIENTS WITHOUT THYROID DISEASE

BY

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Since the work of Roitt and Doniach (1960) and others it is known that the sera of patients suffering from thyroid disorders, especially Hashimoto's disease, often show antibodies to thyroglobulin. The present investigation reports the frequency with which antibodies may be found in subjects not suffering from any apparent thyroid abnormality.

Materials and Methods

The sources of the sera tested were 597 samples sent to the laboratory for performance of the Wassermann test and 700 sent to the blood transfusion service for grouping, the former preserved at 4° C. for a week and the latter at −20° C. The notes were examined of all patients whose sera contained thyroid antibodies, and cases with clinically observed thyroid abnormalities were removed from the main series and made into a subgroup for the purpose of comparing the incidence of complement-fixing antibodies in the two groups (see Table II).

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The sera were estimated by the tanned red cell (T.R.C.) haemagglutination test, using formolized sheep cells coated with purified thyroglobulin, prepared by Dr. A. J. Fulthorpe (Burroughs Wellcome). A screening procedure was developed in order to select sera for full titration, using a platinum loop which could be flamed rapidly between each specimen. A loop of 6 mm. diameter (as used in bacteriology) when dipped into serum was found to pick up a minimum quantity of 0.0025 ml.

0.03 ml. (one drop from a standard pipette) of thyroglobulin T.R.C.s (1 : 100 solution) and 0.03 ml. of normal saline were added to each well of a "perspex" tray. The platinum loop was flamed to white heat, allowed to cool, dipped into the test serum, inspected to see that a film had formed across the loop, then agitated in the measured volume of tanned cells until the film broke. The wire was again flamed, and the procedure could be repeated with further test sera.

This screening method gives a minimum dilution corresponding to a 1 : 10 conventional titre (1 : 20 actual dilution). It was thought that, although many 1 : 5 titres would be missed by this procedure, all titres of 1 : 25 and above should be detected. Ten sera previously established as positive at 1 : 25 and 10 positive at 1 : 250 were screened by the above method, and all were found positive.

Owing to the detection of titres of less than 1 : 5 (the loop could pick up two to three times the minimum) and the presence of heterophil sheep-cell antibodies the screening method produced many false positives, but this did not affect the final result, as all sera found positive were submitted to a full titration (Roitt and Doniach, 1958), preceded by absorption with uncoated formolized control sheep cells. All positive sera (including those from patients with clinically observed thyroid abnormalities) were also examined for complement-fixing antibodies using extracts of thyrotoxic thyroid and other organs. The antigenic activity in the saline extract of thyrotoxic gland is due chiefly to the microsomal fraction. The other antigens were simple saline extracts of each organ. Details of the complement-fixation technique were as described in Roitt and Doniach (1958)—briefly, 2 M.H.D. of complement incubated for one hour with the antigen and test serum, then read after 30 minutes' further incubation with the indicator cells.

TABLE I.—*Tanned Red-cell (T.R.C.) Agglutination—Results by Sex and Age-group*

Age-group*	Female				Male			
	Total Tested	1 : 5	1 : 25	1 : 250	Total Tested	1 : 5	1 : 25	1 : 250
0–19	47	1	0	0	50	0	0	0
20–29	182	1	5	1	120	1	1	0
30–39	132	2	3	1	79	1	0	0
40–44	49	1	2	2	75	3	1	2
45–49	60	1	1	5				
50–54	62	3	3	2	134	1	0	1
55–59	50	4	5	1				
60–69	83	4	7	1	85	2	1	0
70+	41	2	0	0	48	1	1	0
Total	706	19	26	13	591	9	4	3

* Positive sera of patients with recognized thyroid abnormalities have been excluded.

TABLE II.—*Proportion of T.R.C. Agglutination Positive Sera at Each Titre which Contain Antibody to Extracts of Thyrotoxic Gland (C.F.T.+)*

T.R.C. Titre	Non-thyroid Disease		Known Thyroid Abnormality	
	Total in Each Group	C.F.T.+	Total in Each Group	C.F.T.+
1 : 5	27	4+2*	3	2
1 : 25	29	3	3	0
1 : 250	15	1	6	5
1 : 2,500	1	0	3	2
1 : 25,000	1		2	1
Total ..	73	8+2	17	10

* These two patients showed complement-fixing antibodies to organs other than the thyroid—for diagnosis, see text.

Results

1,297 sera were screened and titrated as described. The results, grouped according to sex and age, are shown in Table I and the Charts. 17 positive sera from patients with observed thyroid disease have been excluded from Table I. They are compared with the "normal" group in Table II. As already mentioned, many sera containing a 1 : 5 titre will have been missed by this method, but as there is no reason for thinking that the proportion missed varies between the groups the positive results at this dilution are included. Although the data at 1 : 5 have no absolute value, they can still be used for comparing groups. It can be seen that positive sera at 1 : 25 and above are six times more common among women than among men. At ages 40 to 69, 10% of all women in this series have antibodies to a titre of 1 : 25, 1 : 250, and in one case 1 : 2,500. At 70 and over there are no positives greater than 1 : 5 among the women. In the 20–39 age-group, 8 (5%) positive sera were found among the 174 non-pregnant and 2 (1.5%) from the 140 pregnant females ($\chi^2=2.7$. $P=0.10$).

The number of positive male sera is too small for analysis, but a peak in the 40–49 age-group is suggested, corresponding to the more obvious one in the females.

Complement-fixing antibodies to thyroid at a minimum titre of 1 : 4 were demonstrated in 10 out of 17 sera from patients with known thyroid abnormalities, but in only 10 of the 72 subjects with apparently normal thyroids. Two of these latter 10 gave positive reactions with all other organs, and thus probably contained not the thyroid microsomal antibody but the non-specific anticytoplasmic antibody (Gadjusek, 1958). Of the group derived from the W.R. laboratory, one (a woman aged 54) with a positive T.R.C. agglutination (titre 1 : 5) was also W.R. positive.

Discussion

Hackett, Beech, and Forbes (1960b) gave published figures for the incidence of T.R.C. antibody titres of 1 : 10 and above in a group of 387 mixed medical patients at Adelaide. They found that 25.7% of women aged 30 and over were positive at this titre. Unfortunately their series is not comparable with the one here presented, as the discriminating titre selected is different, the sensitivity of their tanned-cell system is probably greater than here, and 15 of their 68 positives were suffering from "collagen" and allied diseases in which there is a generalized increase in antibody activity. The chief qualitative differences are that in the present series of women a sudden increase in the number of positive sera is found in the fifth decade as against the fourth decade in Adelaide, where they persist into oldest age as against the suggestion of a falling off in the over 70s in this series. (Comparison of the female over 70s with the 40–69 age-group gives $\chi^2=3.38$, $0.05<P<0.1$.) The sex ratio of positives, corrected for the unequal numbers of the sexes in the populations examined, in Adelaide is 1 : 2.5 male to female as against 1 : 4.5 here. (Comparison of actual numbers involved gives $\chi^2=4.65$, $P<0.05$.) If only the 1 : 5 titres are taken into account

the ratio becomes 1:1.75—much closer to the Adelaide figure—and consequently the difference between the two series is probably due to the weaker titres accepted by Hackett *et al.*, at which lower levels the relation between sex and antibody production may be less marked.

It is interesting that the sex ratio of 1:4.5 compares closely with the 1:4 male/female ratio commonly given for clinical myxoedema (Means, 1948). Fig. 3 shows the distribution of age of onset by decades of 107 females suffering from primary myxoedema and/or Hashimoto's disease seen in recent years at the Middlesex Hospital. It can be seen that there is a resemblance between the age distribution of these patients and those of the present series, with a similar peak in the fifth decade.

In another series, Blizzard *et al.* (1960) found agglutinating antibodies in 1.8% pregnant women as against 3% in the general population; but their general group was not a matched population, as it included male and female subjects 17 to 70 years of age.

In the present series, owing to the source of the sera, there are many pregnant women, males healthy apart from possible venereal disease, surgical admissions (routinely blood-grouped), and patients from a large radiotherapy unit. Owing to this bias no special significance can be attached to the diagnoses given in Table III. For example, the apparent prominence of

TABLE III.—*Diagnoses of Patients whose Sera Contained a Titre of T.R.C. Agglutinating Antibodies* 1:250 *and Above*

Intermenstrual bleeding (due to proliferative endometrium)
Fibroids
Broad-ligament cyst
Haemorrhage into ovarian follicle
Squamous metaplasia of cervix
Carcinomatosis (breast)
Hodgkin's disease
Chronic lymphatic leukaemia with multiple transfusions (1 : 25,000)
Varicose veins
Hernia
Gall-stones and carcinoma of uterus (1 : 2,500)
Osteoarthritis of hip
Gastric ulcer
Epilepsy

gynaecological conditions arises because the main source of sera in the middle-aged group, in whom antibodies seem especially common, is almost exclusively from women admitted for gynaecological operations. It has been suggested that there is a relation between disorders of the thyroid and disease of the female genital tract, but this contention is far from proved.

The more common finding of complement-fixing antibodies in patients with thyroid disease than among "normals," despite their both showing agglutinating antibodies, accords with the experience of Roitt and Doniach (1958), who demonstrated that, of those sera containing agglutinating antibodies, complement-fixing antibodies were present in practically all cases of Hashimoto's disease, in two-thirds of spontaneous adult myxoedema cases, in about one-half of thyrotoxics, and in one-seventh of patients with non-toxic colloid goitre. Goudie, Anderson, and Gray (1959) have studied the incidence of complement-fixation in a hospital population not suffering from overt thyroid disease. They found a sex ratio of 1:5 male to female, but the peak frequencies were clearly in the sixth and seventh decades. They were able to examine a number of the thyroids of these patients after death, and found a high correlation between C.F.T. positive sera and areas of lymphocytic infiltration. Their work also correlates well with Simmonds's (1913) observations on lymphocytic islands in the thyroid, as he also found a very definite peak in the sixth and seventh decades, falling off thereafter.

Unlike Hackett, Beech, and Forbes (1960a), who found that 8% of healthy blood donors had positive complement-fixation tests to at least one of a selection of organs, of the 90 sera tested in the present series (all those containing agglutinating antibodies), only two gave complement-fixing antibodies against organs other than the thyroid. One patient had a carcinoma of the cervix with bilateral ureteric obstruction and had been treated by radiotherapy, the other was a pregnant woman aged 29 with a history of recurrent acute arthropathy over the preceding three years. Hackett's method employs a smaller amount of complement, with a consequent greater sensitivity than the method used here. Their thyroid antigen was prepared from normal thyroid tissue and accordingly their results are not comparable with those of the present series, in which the antigen was extracted from thyrotoxic gland.

Summary and Conclusions

It has been established that thyroglobulin antibodies are commonly found in patients with apparently normal thyroids. The age–sex distribution found in subjects with antibodies is very similar to the age-and-sex pattern in patients with myxoedema and Hashimoto's disease, with a maximum in the fifth decade, but both precede by 10–20 years the peak frequency of lymphocytic infiltration and associated positive complement fixation.

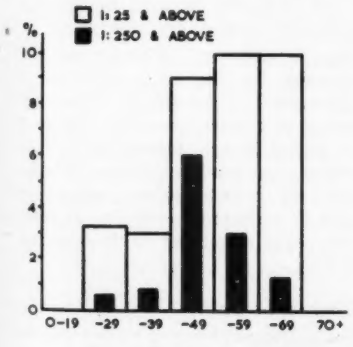

FIG. 1

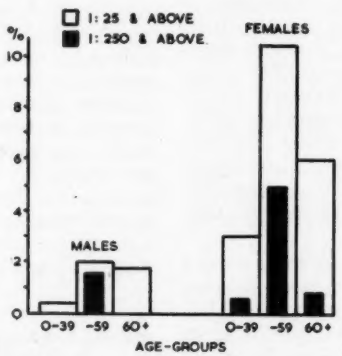

FIG. 2

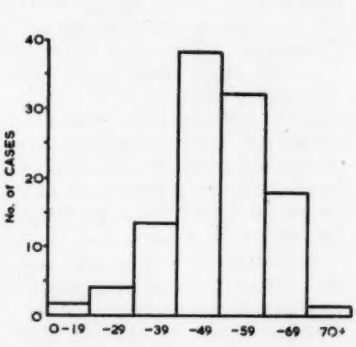

FIG. 3

FIG. 1.—Distribution in decades of women with positive sera 1:25 and above. (Constructed from data in Table I.) FIG. 2.—Comparison in three age-groups between men and women with positive sera 1:25 and above. (Constructed from data in Table I.) FIG. 3.—Distribution of estimated age at onset of 107 patients suffering from hypothyroidism and/or lymphadenoid goitre seen in recent years at the Middlesex Hospital.

The figures reported here show that over 10% of middle-aged women have circulating thyroid antibodies.

Some of these women probably proceed to overt thyroid deficiency with high titres of antibodies, but the factors which influence progression are as yet unknown.

Theoretical considerations apart, it is hoped that the data here presented will provide an empirical basis for estimating the significance of antibody levels in the diagnosis of thyroid disease.

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PHENFORMIN AS ADJUVANT ORAL THERAPY IN DIABETES

BY

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The sulphonylurea group of drugs were the first to be used successfully in the oral treatment of diabetes (Franke and Fuchs, 1955; Bertram *et al.*, 1955). It soon became apparent that these drugs were ineffective in severe diabetics with a tendency to ketosis, and their use is now restricted to milder diabetics who cannot be controlled by simple dietary restriction. Two drugs of this type are in common use—tolbutamide and chlorpropamide. The latter is the more powerful hypoglycaemic agent and has a more prolonged action (Granville-Grossman *et al.*, 1959). However, not all diabetics who might be expected to respond to chlorpropamide do so in practice. Some newly diagnosed diabetics whose urine is free from ketones fail to respond satisfactorily to chlorpropamide, while others who have responded initially begin to relapse into hyperglycaemia gradually after a time.

Phenformin is a diguanide, and earlier trials showed that, although it is a most potent hypoglycaemic agent and sometimes successful where chlorpropamide has failed, it is poorly tolerated when administered at its maximum therapeutic level, often giving rise to gastro-intestinal disturbances (Hall *et al.*, 1958). Its mode of action is uncertain but differs from that of the sulphonylureas (Marble, 1960). Hence, in patients who show an inadequate response to the sulphonylureas, phenformin has been used as an addition to these drugs (Beaser, 1958, 1960; Granville-Grossman *et al.*, 1959; Unger *et al.*, 1960). Given in this way, the dose of phenformin can be reduced sufficiently to avoid gastro-intestinal intolerance.

The purpose of this communication is briefly to review the present overall picture of tablet therapy in a diabetic unit, and, in particular, to define the role of phenformin as adjuvant therapy to the sulphonyl ureas.

Overall Picture

Suitable records were available for 1,450 diabetic patients treated at Whittington Hospital Diabetic Clinic. These were divided into three groups: those controlled by simple dietary restriction alone, those taking tablets, and those requiring insulin. These groups are not static. Many diabetics needing insulin or tablets for initial control later remitted and were managed on simple dietary control (Bloom, 1959). Others who were well controlled for many years on dietary restriction later began to relapse and needed tablets or insulin. Some who were well controlled initially by tablets later relapsed and needed insulin.

The large majority of young diabetics required insulin, and only a few could be controlled on diet or tablets (Table I). In those over 50, however, more than 20% were controlled by oral therapy. The majority of patients controlled by tablets were taking either chlorpropamide or tolbutamide (Table II). In recent years chlorpropamide has been used in preference to tolbutamide in new cases, but patients already satisfactorily controlled by tolbutamide have continued on this therapy. 40 patients, representing 16% of those on oral therapy, or 2.7% of all diabetics, required phenformin in addition to either chlorpropamide or tolbutamide.

TABLE I.—*Treatment of* 1,450 *Diabetics According to Age*

Age:	0–30	31–50	51–70	71+
Insulin ..	111 (87·4%)	150 (52·6%)	210 (31·4%)	137 (37·2%)
Diet alone ..	12 (9·5%)	104 (36·5%)	320 (47·7%)	151 (41·0%)
Tablets ..	4 (3·1%)	31 (10·9%)	140 (20·9%)	80 (21·8%)
Total ..	127 (100%)	285 (100%)	670 (100%)	368 (100%)

TABLE II.—1,450 *Diabetics According to Treatment*

Insulin		608
Diet alone		587
Tablets		255
Chlorpropamide	107	
Tolbutamide	94	
Phenformin	14	
Chlorpropamide plus phenformin	36	
Tolbutamide plus phenformin	4	

Phenformin as Adjuvant Therapy.—Phenformin was used as adjuvant therapy to the sulphonylureas in diabetics showing primary or secondary failure of response to tolbutamide or chlorpropamide. Primary failure was noted in diabetics not responding to diet, and also in diabetics previously taking insulin. Secondary failure occurred in patients who were controlled by tolbutamide or chlorpropamide for at least a month but who then began to relapse on this therapy despite adherence to diet.

Method of Trial

Diabetics Not Responding to Diet and Showing Primary Failure to Respond to Tolbutamide or Chlorpropamide

New cases not severe enough to need insulin were placed on a restricted diet varying from 800 calories a day (80 g. carbohydrate) in very obese patients to 1,500 calories (175 g. carbohydrate) in those of normal weight,

and they were observed each week as out-patients. Patients were taught to test the second specimen of urine passed before breakfast and lunch, and before retiring at night. They used "clinitest" tablets and charted their findings. At each attendance, usually in the afternoon two or three hours after lunch, venous blood was taken for estimation of sugar (Hagedorn and Jensen method). Patients were regarded as well controlled when the urine became free from sugar and the blood sugars were less than 190 mg./100 ml. Tolbutamide 1 g. b.d. or chlorpropamide 500 mg. daily was prescribed only when an adequate trial of dietary restriction failed to lead to good control. Where these tablets also proved unsuccessful, phenformin was prescribed as an addition to previous therapy. If this combination of drugs was unsuccessful the patient was given insulin.

The usual maintenance dose for patients taking tolbutamide and phenformin was 500 mg. of the former and 25 mg. of the latter, both three times daily. In patients taking chlorpropamide and phenformin the usual daily maintenance dose was 350 mg. of the former and 100 mg. of the latter in the form of a slow-acting capsule: before the capsule had become available 25-mg. tablets t.d.s. were prescribed.

Some of these patients were admitted to the ward for in-patient trials as described later.

Patients Previously Controlled by Insulin

Attempted transfer from insulin to tablets was offered to stable diabetics with insulin requirements of less than 30 units a day and where there was no tendency to ketoacidosis. In some patients, however, the attempted transfer was at the patient's request, and sometimes in patients where there seemed little likelihood of success. Diabetics previously controlled on insulin were always admitted to the ward before transfer to oral therapy, since even diabetics on small doses of insulin sometimes became rapidly ketotic when insulin was discontinued. When insulin was omitted, chlorpropamide 500 mg. daily was first administered. Where this failed to control the diabetic state, phenformin was added.

In some of these patients a fuller ward trial was undertaken as described later.

Patients Showing Secondary Failure

These patients had previously been well controlled on either tolbutamide or chlorpropamide, but had begun to show a return of hyperglycaemia and glycosuria despite adherence to diet. Where it was suspected that failure was due to dietary indulgences, the importance of diet was stressed before altering therapy. In some patients admitted to the ward under these circumstances, steady amelioration of the diabetic state occurred on the same tablets and ostensibly on the same diet as was alleged to have been followed at home. In the remainder phenformin was added to the previous therapy and observation continued usually as out-patients.

Separate in-patient trials were conducted on some of these patients.

Results

47 diabetic patients, having failed to respond either to tolbutamide 1 g. b.d. or to chlorpropamide 500 mg. daily, became well controlled when phenformin was added to the previous therapy.

These patients were derived as follows:

1. 18 patients not controlled by dietary restriction had shown a primary failure to respond to the sulphonylurea alone, but became well controlled on the addition of phenformin.

2. 13 patients had been previously well controlled on insulin but showed a return of glycosuria and hyperglycaemia when chlorpropamide was substituted for insulin. Control was re-established when phenformin was added to chlorpropamide. Although insulin requirements had sometimes fluctuated, at the time of transfer one patient was taking less than 20 units, eight were taking between 20 and 30 units, two between 30 and 40 units, and two between 40 and 60 units.

3. 16 patients had responded initially to tolbutamide or chlorpropamide but had gradually relapsed. Three had relapsed within six months, four between six months and a year, six between one and two years, and three between two and three years after the beginning of sulphonylurea therapy. Good control was again established in these patients when phenformin was added.

Of these 47 patients successfully controlled on a combination of a sulphonylurea with phenformin, 7 ultimately relapsed and were transferred to insulin. Table III sets out the length of observation.

TABLE III.—*Length of Observation of Patients on Combined Therapy*

Months :	1–3	3–6	6–9	9–12	12–18	18–24	>24
No. of patients so far controlled (40) ..	5	6	9	7	7	5	1
No. of patients who relapsed (7)	3		2	1	1		

Two patients died during the recorded period, one of carcinoma of the bronchus and one of cerebral haemorrhage. There was no evidence that current therapy contributed to the cause of death.

Ward Trial

There were two possible explanations for the successful addition of phenformin to chlorpropamide in patients responding poorly to chlorpropamide alone. The continued use of chlorpropamide in these patients could have been irrelevant and the improved response simply due to phenformin. Alternatively, phenformin could have exerted an additive hypoglycaemic effect to that of chlorpropamide, and the resultant normoglycaemia could have been partly due to each. Hence a ward trial was undertaken of a group of patients who showed an inadequate response to chlorpropamide. These patients were observed in the ward for a minimum of five days while taking chlorpropamide, and venous blood sugars were estimated before lunch. Urinary sugar was measured four-hourly. Where glycosuria persisted and blood sugars remained raised above 190 mg./100 ml., chlorpropamide was discontinued, and phenformin 100 mg. once daily or 25 mg. t.d.s. was given in its place. If there was no response to this drug alone after a minimum of five days, both drugs were given together in the same dosage as previously.

Results

In all, 36 patients who had failed to show an adequate response to chlorpropamide were investigated in this way.

Nine patients who failed to respond to chlorpropamide were successfully controlled on phenformin. At a dose level of 25 mg. t.d.s. or 100 mg. daily the urine became

sugar-free and blood sugars near normoglycaemic. Fig. 1 shows an example of a patient who responded in this way.

14 patients who failed to respond to either drug separately showed good response when the tablets at the same dosage were given together. Fig. 2 provides an example of this response. These 14 cases are included in those previously described as having responded to combined therapy.

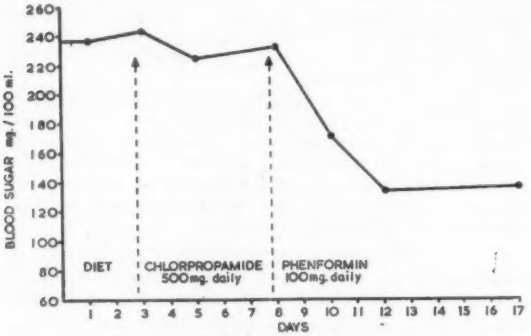

FIG. 1.—Graph of a patient who responded to phenformin after failure with chlorpropamide.

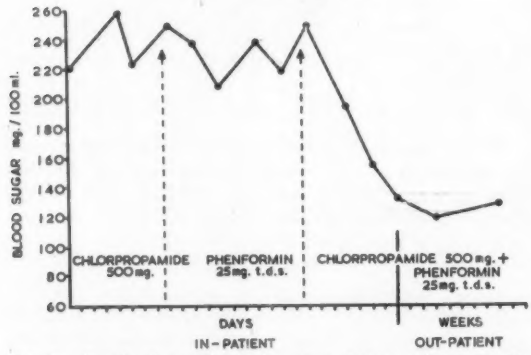

FIG. 2.—Graph of a patient who responded to chlorpropamide and phenformin given together after failure to respond to the drugs given separately.

13 patients failed to respond to either drug separately or when given in combination, and these patients were transferred to insulin. The number of patients who failed tablet therapy in this manner is of no real significance, since it included some diabetics who were thought unlikely to respond to oral therapy.

Slow Disintegration Capsules

Phenformin given as a single large dose will suppress the blood sugar in from four to ten hours, with maximal effect at six hours (Hall *et al.*, 1958). This means that when smaller doses are used the tablets must be administered two or three times a day to establish adequate control. To overcome this difficulty, capsules have been prepared which contain granules of phenformin mixed with shellac, with the aim of allowing a gradual release of the drug during the day. In order to test the efficiency of these capsules, patients were maintained on a measured diet during the trial, and blood and urinary sugars were measured daily. After a period on tablets, 25 mg. q.d.s. or 50 mg. b.d., the capsules were introduced as a single 100-mg. dose in the morning. On one day during each treatment blood sugars were taken at intervals during the day. As shown in three cases (Table IV), the blood sugars were broadly similar whether the patient was taking the capsule once each morning or the tablets during the day.

TABLE IV.—*Three Subjects, on Two Different Days, Treated with Phenformin Tablets as Multiple Dose or as Single Slow Disintegration (S.D.) Capsule. Blood Sugars Expressed in mg./100 ml.*

Case		a.m.		p.m.			a.m.		p.m.	
		7.30	11.30	5·30	12		7.30	11·30	5·30	12
A	25 mg. q.d.s.	160	138	156	146	100 mg. S.D.	160	114	126	116
B	50 mg. b.d.	164	148	170	152	100 mg. S.D.	172	154	180	186
C	100 mg. S.D.	158	140	188	171	25 mg. q.d.s.	160	167	207	155

Out-patients taking phenformin 25 mg. t.d.s. or 50 mg. b.d. were transferred to 100-mg. capsules daily. No deterioration in the diabetic state could be detected after this transfer.

Drug Tolerance

In the main, both tolbutamide and chlorpropamide were well tolerated as previously recorded (Granville-Grossman *et al.*, 1959).

Two elderly patients taking chlorpropamide 500 mg. each morning became confused at night. Even when the dose was reduced to 100 mg. daily confusion persisted for several nights before improvement occurred, and was assumed to be due to hypoglycaemia.

Given at a dose not exceeding 100 mg. daily, phenformin gave rise to minimal pejorative effects. Mild nausea, anorexia, and an unpleasant taste in the mouth were the commonest complaints, elicited as a rule on direct questioning. Nevertheless, in some patients these effects were troublesome enough to warrant discontinuance of this treatment. Some of the patients who had experienced mild nausea when taking phenformin tablets claimed improvement in this respect when transferred to the capsules.

Discussion

Chlorpropamide is both effective and well tolerated by most diabetics who fail to respond to dietary restriction but who do not become ketotic. Whether these patients are newly diagnosed or whether they have been controlled previously on a small dose of insulin, normoglycaemia can usually be maintained by a dose of 500 mg. a day, later reduced to 350 mg. or less. Nevertheless, many diabetics expected to respond to this tablet therapy in practice fail to do so. Others who respond initially to chlorpropamide begin to relapse after a time despite continued adherence to a diet. It is in such cases that phenformin offers the opportunity of prolonging oral therapy without recourse to insulin. Phenformin is a powerful hypoglycaemic agent, but it so often gives rise to gastro-intestinal intolerance when administered in the maximum therapeutic dose that it is not as suitable as the sulphonylureas for general use. However, when given at a dose of 100 mg. a day it is reasonably well tolerated by most, and can be administered conveniently in the form of a single slow-disintegration capsule. Although this is a comparatively small dose of phenformin it effectively controlled hyperglycaemia in some diabetics in whom chlorpropamide was inadequate. In a greater number of diabetics in whom chlorpropamide was unsatisfactory, however, substitution by phenformin was ineffective, but control was obtained when the two agents were administered together. Hence it would seem

convenient in patients responding poorly to chlorpropamide to try the addition of phenformin before recourse to insulin.

Diabetes is a progressive disease, though the rate of progression varies greatly. It is not surprising that some patients at first controlled by the sulphonylureas slowly began to relapse, and this was equally true of patients controlled on combined therapy. In some patients the introduction of combined therapy has meant no more than a delay before insulin was introduced. Nevertheless in other patients treatment by combined therapy has been prolonged, and has been particularly welcomed by elderly patients who would otherwise have required insulin.

Whereas it seems clear that oral therapy as at present described is capable of maintaining normoglycaemia, it remains open to question whether this is sufficient to prevent the degenerative complications so commonly seen in diabetics poorly controlled on insulin, since these complications could possibly be due to factors other than hyperglycaemia. However, quite apart from ultimate complications, hyperglycaemia leads to troublesome symptoms and predisposes to infection. In the present state of our knowledge, these seem valid reasons to justify the use of oral therapy in responsive patients.

Summary

Of 1,450 diabetic patients attending a clinic, 587 (40.4%) were controlled on simple dietary restriction, 608 (42%) required insulin, and the remaining 255 (17.6%) took oral hypoglycaemic agents.

Diabetics deemed suitable for oral therapy who failed to respond to chlorpropamide were given phenformin in small doses as an alternative or as adjuvant therapy. Of 23 such patients, 9 responded to phenformin alone but 14 responded only when the phenformin and chlorpropamide were given together.

Phenformin when administered in a single daily 100-mg. slow-disintegration capsule appeared to offer as effective clinical control as when given in divided doses as tablets.

Our thanks are due to Dr. K. Boheimer, of Bayer Products, for the supply of phenformin capsules ("dibotin" sustained release capsules).

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Among the 3,334 visitors to Coventry who were treated by local doctors last year were an Ethiopian, a Kuwaitian, a Libyan, a Venezuelan, a Norwegian, three Yugoslavians, and four Sudanese. These figures are given in the annual report of the Coventry Executive Council of the Health Service. On January 1 this year 308,359 persons were on Coventry doctors' lists. On April 1 there were 133 doctors in the city and 84 surgeries. It was stated that five people lost dentures while swimming, one lost them "overboard," six threw them in the fire, and two had them destroyed by dogs. (*Birmingham Post*, May 1.)

BARIUM STUDIES IN THE AGED

BY

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As the possibilities of treatment in the field of geriatrics increase, more and more elderly patients will be submitted to radiological examinations. Some examinations can be carried out almost as easily in the old as in the young. Others, such as the investigation of the alimentary tract by means of barium meals and enemas, may be difficult because of the patient's physical frailty or disability or because his mental state prevents his effective co-operation. Moreover, the barium examinations and the preparation entailed may be distressing for the patient. Barium studies in a series of aged patients have therefore been reviewed in order to determine in how many the results were of practical value and in how many of merely academic interest.

The patients investigated had been treated in the geriatric unit during the past five years and were 70 or more years old. The oldest was 93, and the average age was nearly 80. 148 barium studies (102 meals and 46 enemas) were undertaken on 129 patients (40 men and 89 women). Thirteen patients had both a barium meal and an enema. Five patients had two barium meals and one had two barium enemas. In six cases a meal was attempted but was unsatisfactory because the patient was either not able to co-operate or proved unfit for the examination.

Barium Meals

The findings in the patients examined by barium meal are shown in Table I.

Clinical Diagnosis of Peptic Ulcer (20 Patients).—This diagnosis was confirmed in 11 patients (7 gastric ulcers, 4 duodenal ulcers). An additional 16 cases of

TABLE I.—*Radiological Findings in 97 Patients (102 Barium-meal Examinations) Grouped According to Diagnosis or the Indication for Investigation.*

Radiological Findings	Provisional Clinical Diagnosis or Indication for Investigation					
	Peptic Ulcer	Carcinoma of Stomach	Gastro-intestinal Haemorrhage	Dysphagia	Hiatus Hernia	Total
No abnormality discovered	8	15	15	6	2	46
Gastric ulcer	7	2	10		1†	20
Duodenal ,,	4		3			7
Hiatus hernia		1	6	3	5	15
Carcinoma of stomach		3				3
Carcinoma of oesophagus				2	1†	3
Duodenal diverticulum			2*			2
Oesophageal diverticulum	1				1	2
Neurological disorder				1		1
Achalasia of cardia				1		1
Pressure on oesophagus by dilated aorta		1				1
Situs inversus			1*			1
	20	22	37	13	10	102

* Included among the 15 cases assumed to have no abnormality.
† Associated with hiatus hernia.

peptic ulcer (13 gastric, 3 duodenal) were found in patients with other clinical diagnoses. Thus 27 peptic ulcers (20 gastric, 7 duodenal) were found in the whole series. Five of the 20 gastric ulcers were "giant" ulcers (Strange, 1959). 14 of these patients were discharged well after medical treatment. Two were discharged well after surgical treatment: one had an elective partial gastrectomy ; the other, who had had haematemesis and a negative barium-meal examination, had a further haematemesis, for which an emergency partial gastrectomy was performed when the gastric ulcer was found. Four patients died ; one after sudden general deterioration in hospital ; one from unrelated conditions ; one after continued melaena—this patient was unfit for operation ; and one who deteriorated while having medical treatment, and in whom it was found at necropsy that the ulcer was malignant. The seven patients with duodenal ulcer were all discharged well.

Clinical Diagnosis of Carcinoma of Stomach (22 cases).—In only three cases was this diagnosis confirmed by barium-meal examination. No cases of gastric carcinoma were found at barium-meal examinations performed in patients with other clinical diagnoses, although one radiologically benign ulcer was found at necropsy to be malignant. Of the three cases thought at barium-meal examination to have gastric carcinoma, one was found at operation to have a non-resectable carcinoma of the pancreas invading the pyloric antrum, another refused operation, and in the third, with clinically obvious metastases in the liver, operation was not advised. The final diagnosis in two patients with anorexia, loss of weight, and abdominal pain was pernicious anaemia.

Clinical Diagnosis of Gastro-intestinal Haemorrhage (? Cause) (34 Cases).—Nine patients presented with haematemesis or melaena. Three found to have a gastric ulcer and one found to have a duodenal ulcer were discharged well after medical treatment. One patient with a gastric ulcer had recurrent haemorrhage, was never fit for operation, and died in hospital. Of four patients in whom no abnormality was found at radiological examination, three were discharged well after medical treatment. The fourth, already mentioned, had a further haematemesis, and at emergency partial gastrectomy a gastric ulcer was found which had not been seen at the barium-meal examination. Twenty-five patients had anaemia with occult blood in the stools. Six found to have peptic ulcers (four gastric, two duodenal) were discharged well after medical treatment. One patient with a gastric ulcer died in hospital from unrelated conditions. A woman aged 93, who could not be persuaded to drink the barium, died in hospital and was found at necropsy to have a giant gastric ulcer. Of six patients shown to have hiatus hernia, which may or may not have been the cause of the haemorrhage, four were discharged well after medical treatment, one is still alive and well in hospital, and one died from an unrelated condition. The 11 patients in whom no abnormality was present included one in whom a satisfactory examination was impossible on account of Parkinsonism, who died in hospital, and in whom at necropsy no gastro-intestinal abnormality was found. The other 10 were discharged well after medical treatment.

Clinical Diagnosis of Dysphagia (? Cause) (13 Patients).—One patient found to have cardiospasm was discharged well on medical treatment. Of two found to have carcinoma of the oesophagus, one died the day after oesophagoscopy. The other was thought unfit for resection of the growth and was discharged with a view to readmission when the dysphagia became severe enough to justify intubation, but never returned. In one elderly woman dysphagia, starting after a cerebrovascular accident a few weeks before, improved as she recovered. Hiatus hernia was present in three of these patients. Two were discharged, one with less dysphagia and the other free from symptoms. In the third patient, whose dysphagia was of sudden onset, there was a complete hold-up of barium near the lower end of the oesophagus. A few days later swallowing was normal and there was no hold-up of barium. The dysphagia was assumed to be due to impaction of food above the herniated stomach. In six patients no definite abnormality of the oesophagus or stomach was found. In three, however, conditions were present which might well have been the cause of the dysphagia—motor neurone disease in one and heart failure in another (Keates and Magidson, 1955). The third was found later to be suffering from bronchial carcinoma, which was probably the cause of the dysphagia, though radiological evidence of this had not been detected. Of the other three, in one no cause for the dysphagia was found at necropsy and two were discharged still complaining of dysphagia.

Clinical Diagnosis of Hiatus Hernia (8 Patients).—The diagnosis was confirmed in five of these patients. In one there was an associated peptic stricture ; in another there was a coincident carcinoma of the upper thoracic oesophagus, and in another a gastric ulcer. Six patients found radiologically to have hiatus hernia, in whom the indication for the examination was anaemia with occult blood in the stools, are considered with the cases of gastro-intestinal haemorrhage. Three cases are considered among those presenting with dysphagia. One patient with symptoms suggesting carcinoma of the stomach was found to have a sliding hiatus hernia, but the final diagnosis was pernicious anaemia ; an atypical blood-picture had given rise to difficulty in diagnosis.

Barium Enemas

The findings in the patients examined by barium enema are shown in Table II. By "examination impossible" is meant that the patient was unable to retain the barium in spite of the use of an inflatable balloon in the rectum.

Clinical Diagnosis of Gastro-Intestinal Haemorrhage (? Cause) (7 Patients).—Two patients with anaemia and occult blood in the stools, who had had a negative

TABLE II.—*Radiological Findings in 45 Patients (46 Barium Enemas) Grouped According to Diagnosis or the Indication for Investigation.*

Radiological Findings	Provisional Clinical Diagnosis or Indication for Investigation			
	Carcinoma of Colon	Diverticulitis	Gastro-intestinal Haemorrhage	Total
No abnormality discovered ..	14	3	4	21
Diverticulitis ..	2	7	1	10
Diverticulosis ..	3	5	1	9
Carcinoma of colon	1*			1
Diaphragmatic hernia (colon in chest)	1*			1
Examination impossible ..	3		1	4
	24	15	7	46

* Also had diverticulitis of sigmoid.

barium-meal examination, also had a negative barium enema. One was discharged well and the other died of chronic myeloid leukaemia. Of two other patients examined on account of anaemia, one had a hiatus hernia and diverticulitis and the other had a duodenal ulcer but no abnormality in the colon. Of three patients who had not had a barium meal, one who had blood in the stools and a negative barium enema had piles and was discharged well; one who had melaena had a negative barium enema and died later of chronic myeloid leukaemia; and in one the examination was impossible and at necropsy a carcinoma of the caecum was found.

Clinical Diagnosis of Carcinoma of Colon (23 Patients).—This diagnosis was made radiologically only once; at operation the lesion was found to be an argentaffinoma of the caecum. In one patient with marked diverticulosis a carcinoma of the transverse colon, obvious in retrospect, was missed and was found later at operation for acute obstruction. In another patient, already mentioned, examination was impossible, and a carcinoma of the caecum was found at necropsy.

Clinical Diagnosis of Diverticulitis (15 Patients).—The clinical diagnosis of diverticulitis was confirmed radiologically in seven cases. A further three cases of diverticulitis were found in the whole series. All 10 patients were treated medically; nine were discharged home improved, and the condition of the last, who had a recto-vaginal fistula, remained unchanged.

Discussion

The results of hospital treatment in these 129 patients show that 91 (70.5%) were discharged from hospital either free from symptoms or improved. The other 38 were still in hospital at the time of the survey or had died. The fact that over 70% of these patients were clinically improved may be taken as an indication of the value of hospital treatment in this group with gastro-intestinal disorders, whose average age is very high—nearly 80 years. Such satisfactory results could be obtained only by instituting treatment on the basis of an accurate diagnosis. In so far as the barium-meal and barium-enema examinations helped to make possible the correct diagnosis, they would seem to be valuable procedures even in the very old.

Some patients are so frail or disabled that even a barium-meal examination is a trial for them, and no amount of pre-operative treatment would make them fit for surgery. Such patients might well be treated on the basis of the clinical diagnosis alone. With these exceptions accurate diagnosis is as necessary in the elderly as in other age-groups. A neoplasm which may be the cause of the symptoms may be operable. A peptic ulcer, if present, should be treated until healed, and follow-up barium-meal examinations are desirable because complete relief of symptoms often precedes healing. An ulcer in an elderly patient may require elective surgical operation, and if emergency surgery is ever required for haematemesis it is helpful at operation if the site and size of the ulcer are known. These considerations apply particularly to giant gastric ulcer, which Strange (1959), in the largest reported series, has shown to have its maximum incidence in the older age-groups.

A definite diagnosis has been helpful in these elderly patients apart from the possibility of operation. Some with peptic ulcer were affected also by rheumatoid arthritis, and here it was appreciated that phenylbutazone and steroids must be avoided. In others, the presence of hiatus hernia was a cogent reason for keeping the patients out of bed as much as possible in order to avoid or at least to minimize reflux oesophagitis. In fact, in four of our patients with hiatus hernia, symptoms thought to be due to the hernia began after confinement to bed for another condition. In others, again, a negative barium-meal examination made possible a more confident diagnosis of psychogenic disorder.

All the barium-meal examinations of this series are thought, on review, to have been justified except in the one patient with clinically obvious metastases in the liver in whom the demonstration of the primary growth in the stomach was of only academic interest. Many barium enemas, however, might have been avoided by the application of principles suggested by Haggie (1952). He reviewed all cases of carcinoma of the colon—apart from cases of carcinoma of the rectum—seen at the London Hospital over a three-year period from the point of view of method of diagnosis. 110 cases were studied. About one-third presented as acute or subacute intestinal obstruction or after acute perforation. Of the remaining 75 cases, one had ascites and one had generalized carcinomatosis. All the others had passed blood per rectum, or had a mass palpable per abdomen or per rectum, or had a growth visible on sigmoidoscopy.

Haggie pointed out also that a high proportion of barium-enema examinations are negative. In one year, out of 227 such examinations, 163 showed no abnormality. Most of them had been given to exclude carcinoma of the colon in patients without abnormal signs. With one possible exception none had developed carcinoma two years later. It seemed from this investigation that the greatest value of the barium-enema examination was to locate the site and nature of a mass already felt. Haggie concluded that it is highly improbable that a patient complaining only of colonic symptoms without blood in the stools, and showing no abnormal physical signs and no abnormality on rectal examination or on sigmoidoscopy, would be found to have carcinoma of the colon if a barium enema is given. He stated that this applies also to what Bockus has called the "much bally-hooed phenomenon" of alternating diarrhoea and constipation which is usually due to the misuse of aperients.

An attempt was made to confirm Haggie's conclusions by a review of a series of consecutive cases of carcinoma of the colon seen in this hospital. 123 cases were considered. Of these, 39 had presented as acute intestinal obstruction, nine after acute perforation, and one as acute appendicitis. Among the other 74 cases there was only one exception to Haggie's rule—a case of carcinoma of the caecum in a patient who had not passed macroscopic blood per rectum and without a palpable abdominal mass.

With Haggie's and these observations in mind the barium-enema examinations of the present series were analysed. Assuming the validity of Haggie's criteria, out of the 45 patients examined by barium enema, the examination was indicated in 16 who had either passed blood per rectum or had a palpable mass. In five who had passed blood per rectum no evidence of carcinoma or diverticulitis was found. Among the 11 who had a palpable abdominal mass there were three malignant tumours of the colon and one case of diverticulitis of

the sigmoid. Among the 29 cases in which, according to these criteria, there was no need to consider carcinoma of the colon, there were 15 with no abnormality, five with diverticulosis, and nine with diverticulitis. All the cases of diverticulitis were treated medically. As the surgical treatment of uncomplicated diverticulitis is rarely undertaken in the elderly, the question arises whether confirmation of the diagnosis by barium-enema examination serves any useful purpose. Haggie was concerned with the value of this examination in the diagnosis of carcinoma of the colon. It is suggested that this approach might apply also to the diagnosis of diverticulitis, at least in the elderly, and that a barium enema is rarely indicated if the patient has not passed macroscopic blood in the stools or has no abnormal physical signs, and if no abnormality is found on rectal examination or on sigmoidoscopy. To make it even less likely that the occasional case of carcinoma will be missed we would add "and if the stools are negative for occult blood." If Haggie's approach had been applied in our 45 patients examined by barium enema, 29 would have been spared the enema, so far as we know without ill effect. Even with our proposed additional indication for barium-enema examination—a positive occult blood test—at least 10 in whom the test was negative would have been spared an enema and probably some if not all of another seven in whom the occult blood test was not done.

Apart from the discomfort of a barium enema and especially of the preparation involved, the examination is not free from risk. A fatal case of barium sulphate embolism is reported by Truemner *et al.* (1960). Cases of retroperitoneal emphysema due to barium enema followed by air insufflation have been recorded by Pyle and Samuel (1960) and by Brunton (1960). The number of published complications of the barium enema reviewed by Pyle and Samuel is formidable. In both these papers the authors stress the special risk in the older age-groups.

It is concluded that in spite of the effort involved for many old, frail, and disabled patients, the barium-meal examination is a useful diagnostic procedure in the aged. In many of these patients, however, the more distressing barium enema might reasonably be avoided.

Summary

102 barium-meal and 46 barium-enema examinations carried out on patients in a geriatric unit are reviewed, with special reference to whether or not the examinations might have been avoided. The barium-meal examinations were found to be surprisingly valuable. There is scope for reducing the number of barium-enema examinations performed, which is desirable in view of the distressing preparation involved and the occasional complications that occur.

We are grateful to Dr. Stachurko, who was responsible for many of these barium examinations; to Dr. T. St. M. Norris and Mr. J. M. Davis, who read the manuscript and made helpful suggestions; and to Mrs. C. Carlin and Mrs. G. Mercer, the *x*-ray department staff nurses, but for whose kindness and sympathy these old people would have found their examinations even more of a trial.

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CORTICAL MASTOIDECTOMY IS STILL NECESSARY

BY

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Since the advent of antibiotics surgical intervention in acute middle-ear and mastoid disease has tended to decrease. Perhaps the time has now arrived to review this policy.

Nowadays, with the changing pattern of response of bacterial organisms to antibiotics and the problems associated with antibiotic-resistant strains, a different picture of mastoid infections seems to be emerging. An increasing number of cases of inadequate response to appropriate antibiotic therapy is being reported in all departments of medicine. There is constant reference to such problems as unresolved pneumonia and persistent infections of the urinary tract. Over the past 18 months we have seen a number of acute mastoid infections which have shown little if any response to antibiotic therapy.

In this article I have attempted an analysis of a series of cases in which the operation of cortical mastoidectomy was performed. In several it will be seen that there were some of the classical indications for operation, such as facial palsy, lateral sinus thrombosis, and otitic meningitis. However, most operations were performed because of the inadequate response of the infection to drug therapy. It is felt that these cases have proved the value of surgical intervention in the control of this new aspect of mastoid infection.

Cases in the Series

During a 12-month period as registrar to the ear, nose, and throat unit in Northampton General Hospital I have personally performed 13 Schwartze-type operations. This hospital serves a district of some 250,000 people. This gives an idea of the relative incidence of the problem in a fairly healthy Midland community. All the cases occurred during the winter months and the average age of the patients was 7 years. The oldest child was 15 years and there were four children under 2 years. With the exception of one infant in whom the mastoid cavity became reinfected, a satisfactory result was obtained in all cases. Even this child settled eventually, although several months passed before she was finally discharged from hospital.

Table I shows those cases in which there was a classical indication for surgical intervention. All these children had been treated with antibiotics before admission to hospital and their complication developed while under antibiotic therapy.

With the exception of Case 1, all these children recovered quickly after a relatively short stay in hospital. At follow-up several months later they had good hearing and dry, intact tympanic membranes. Case 1 later had a successful excision of his cerebellar abscess (neurosurgical unit, Radcliffe Infirmary, Oxford). There is a possibility that this complication might have been prevented by an even earlier drainage of his mastoid infection, as he presented the problem of an acute flare of a chronic suppurative otitis media. However, there can be little doubt that the indication for operation was

urgent in each case. The findings at operation have justified the procedure and there has been a rapid recovery with preservation of function in all these cases.

The other nine cases operated upon (Table II) present a new and interesting aspect of the problem of acute mastoiditis. No. 8 is the only unsatisfactory case among these. This infant had a recurrence of the mastoid infection two months after the original Schwartze operation. At this stage the cavity was reopened and found to be full of chronic indolent granulations. These were curetted clear and the wound was left open to heal from the base. This child was several months in hospital before she was finally discharged. However, at the time of writing, her ear-drum was intact and she seemed to hear satisfactorily. It should be stressed that this was a most unusual occurrence and that it was the only time in 15 years in this hospital where such a procedure was adopted.

Comment

On analysis of Table II certain facts become obvious. In the first instance, all these children were treated with antibiotics. Five of the nine had a prolonged trial in hospital under bacteriological control. There is no doubt about the use of the most appropriate antibiotic, its adequate dosage, or the necessary duration of its course. It can be seen that in several instances no growth was obtained from the cultures of those cases treated with a heavy onslaught of antibiotic before admission to hospital. In Cases 5 and 12 a subsequent course of a second drug was given in hospital when there was no response after a full course of the first antibiotic. Both these children had cultures of haemolytic streptococcus sensitive to penicillin and chloramphenicol. We feel quite confident that a fair trial of antibiotic treatment was given in each case. Surgery was embarked upon only when it was realized that the infection was not being controlled and was showing no evidence of settling under antibiotics.

The next fact to emerge from these cases was the uniformly unsatisfactory response of the infections to antibiotics. In several instances the infection recurred within a day or two of cessation of the first course of the antibiotic. In two cases the signs of acute mastoiditis developed while the child was under appropriate antibiotic treatment.

It should be emphasized that many of these cases had only minimal signs of mastoid involvement. The paucity of physical signs in a case harbouring a widespread underlying mastoid infection is often surprising. In all

TABLE I

Case No.	Sex	Age in Years	History	Admission	Culture	Treatment	Findings	Course
1	M	14	Chronic discharge for 2 years. Recent acute ear treated with penicillin	Acute mastoid and meningitis after four days	Diphtheroid organisms	Penicillin and cortical mastoidectomy	Perisinus abscess	Later developed cerebellar abscess, treated successfully
2	F	11/12	Acute mastoid 2 weeks before. Treated with tetracycline	Subperiosteal abscess	No growth	,, ,,	Subperiosteal abscess	Short hospital stay
3	M	4	Discharging ear for 3 weeks. Treated with penicillin V for 10 days	Acute mastoid and severe toxaemia (vomiting, headache)	*Staph. aureus* (penicillin-sensitive)	Chloramphenicol and cortical mastoidectomy	Lateral sinus thrombosis	,, ,,
4	F	9	Aural discharge for three days	Acute mastoid and facial palsy after three days	Haem. strep. (penicillin-sensitive)	Penicillin and cortical mastoidectomy	Subperiosteal abscess (pus in cells)	Satisfactory

TABLE II

Case No.	Sex	Age in Years	History Before Admission	On Admission	Culture	Treatment	Findings	Course O.P.D. Follow-up
5	F	15/12	Right acute otitis media for 2 weeks. Penicillin and tetracycline given	Right acute otitis media—haem. strep. culture. Penicillin for 7 days. Then chloramphenicol for 8 days	Haem. strep. (penicillin- and chloramphenicol-sensitive)	Right cortical mastoidectomy	Widespread infection, with granulations	Satisfactory hearing; ear-drum normal
6	M	5	Aural discharge and deafness for 2 years. Penicillin V given previously	Acute mastoiditis	Haem. strep. (penicillin sensitive)	Cortical mastoidectomy and penicillin I.M.I.	Frank pus	Hearing and ear-drum normal
7	F	9	Earache and discharge for 2 weeks. Full course of tetracycline	,, ,,	No growth	Cortical mastoidectomy and penicillin	Extensive granulations	,, ,,
8	F	16/12	Left aural discharge for 3 days, left acute mastoiditis for 1 day	Penicillin for 6 days—settled; then developed acute mastoiditis again	,, ,,	Cortical mastoidectomy and oxytetracycline	Diploic process. Some pus. Caries mastoid cortex	Reinfected two months later
9	F	7	Left acute otitis media. Treated in hospital with penicillin for 1 week—settled	Profuse discharge on second admission, 2 days after discharge from hospital	Haem. strep. (penicillin-sensitive)	Cortical mastoidectomy and penicillin	Widespread granulations	Hearing and ear-drum normal
10	F	6	Right aural discharge for 2 weeks. Treated with penicillin	Aural polypectomy. Persistent aural discharge. Penicillin given for 7 days	No growth	Cortical mastoidectomy	Widespread granulating chronic infection	,, ,,
11	F	4	Discharge and deafness intermittently for 3 months. No accurate information on antibiotics	Left acute mastoiditis for 24 hours	*Staph. aureus* (chloramphenicol-sensitive)	Cortical mastoidectomy and chloramphenicol	Chronic granulations	,, ,,
12	F	15	Left acute otitis media for 2 days	Penicillin for 7 days. Chloramphenicol for 10 days. Persistent discharge	Haem. strep. (penicillin and chloramphenicol-sensitive)	Cortical mastoidectomy	Pus ++ in loculated mastoid tip cell	,, ,,
13	F	2	Left acute otitis media. Treated with antibiotics for 2 months intermittently	Acute mastoiditis		,, ,,	Extensive necrosis of mastoid cortex. Tip granulations ++	No follow-up as yet

such cases under antibiotic therapy, any tenderness or softening over the mastoid process should be regarded with suspicion. A profuse and persistent aural discharge is virtually pathognomonic of the spread of the infection to the mastoid cells. If a child develops such signs while under antibiotic treatment it would seem that immediate cortical mastoidectomy is indicated.

Perhaps the most striking characteristic of these children has been the similarity of the operative findings. In almost all cases there was evidence of infection spreading extensively through the mastoid cells. The cell system was occupied by a haemorrhagic granular process with frank granulations growing in many cases. Several showed a marked osteolytic character to the infection with dissolution of the mastoid cortex leaving a cavity occupied by indolent granulations. It was generally a simple matter to curette the soft chronically infected bone clear of disease.

The next point in the analysis of this series is the satisfactory result obtained. These children were discharged from hospital on an average of 12 to 18 days after operation. I have seen them all, except one recent case still in hospital at the time of writing, for follow-up two months after operation. They all have normal hearing and the tympanic membranes on the affected side are dry and clean.

Discussion

It should be stressed that all these patients were children. There would seem to be a strong case for referring all children with acute otitis media which has not resolved after antibiotic therapy for assessment with the view to surgery. Radiological investigation of the mastoid process is often helpful in those cases presenting minimal symptoms and signs of acute mastoiditis. When the infection has persisted for over 10 days there is almost always positive radiological evidence of its spread to the mastoid process.

The main interest in these cases has been the demonstration of this new variety of subacute mastoiditis arising out of unsatisfactory resolution of an acute mastoid infection. These cases may become increasingly common, and one should have this in mind where an acute middle-ear infection fails to respond adequately to antibiotics.

Surgery is highly advisable if these cases are to be treated successfully and their morbidity is to be minimized. It would seem that the persistence of such an infection may lead to chronic mastoiditis and eventually chronic suppuration in the middle ear, as well as to possible intracranial complications. This path of events should be avoided at all costs. As the Schwartze type of operation is a relatively simple procedure, its value in avoiding such a sequence of events is enormous.

The particular interest for the general practitioner should be an awareness of this problem. He should refer all acute middle-ear infections which have failed to respond after 10 days of adequate antibiotic therapy for consultant opinion. If the consultant is conscious of this problem, a timely cortical mastoidectomy will prevent a prolonged stay in hospital and the possibility of chronic middle-ear infection and deafness in the patient is diminished.

Summary

A series of 13 children in whom there was an inadequate response of acute mastoid infections to antibiotics is presented. A widespread subacute infection was seen in nine of these cases. The uniformly satisfactory progress of these children after cortical mastoidectomy is shown. The necessity for careful assessment from a surgical viewpoint is made where acute otitis media in a child does not respond satisfactorily to antibiotic therapy.

I am indebted to Mr. Charles Gledhill for permission to do this work and for his encouragement and help in treating these cases.

MECHANISM AND SIGNIFICANCE OF ERYTHROCYTE SEDIMENTATION RATE

BY

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The earlier hypotheses on the causes of raised erythrocyte sedimentation rate require re-examination. The negative surface charge of the erythrocytes is not altered in bloods with a high sedimentation rate, nor are there always definite quantitative alterations in the distribution of the plasma protein fractions, and we have seen human plasmas with a normal distribution of the proteins which were associated with a raised sedimentation rate. Riva (1957) has already noted that a number of plasmas with a normal albumin/globulin ratio are associated with a high sedimentation rate, and vice versa. Thus an increase in fibrinogen or γ-globulin is only coincidental to a high sedimentation rate and not its cause. Fractionation of normal and high-sedimenting plasmas by means of ammonium sulphate precipitation or preparative paper electrophoresis has shown that the phenomenon is caused by specific proteins (Ruhenstroth-Bauer, 1957, 1959; Ruhenstroth-Bauer, Brittinger, Granzer, and Nass, 1960) (see Table).

By both methods protein fractions could be obtained which at a concentration of 1–2% caused a high sedimentation rate provided supplements such as 0.6% dextran had been added. The supplements by themselves had no effect, and the proteins which produce the increase in sedimentation rate behave, therefore, like incomplete antibodies. Except for fibrinogen, normal plasma contains no fractions which increase the sedimentation rate, and fibrinogen by itself is effective only at concentrations that are rarely seen even in pathological conditions. Investigations of the role of fibrinogen indicated in all cases that its contribution to the sedimentation rate was small. Thus serum from a blood with a high sedimentation rate had a diminished effect compared with that of the analogous plasma (Ruhenstroth-Bauer *et al.*, 1960), and a high sedimentation rate is therefore due to specific serum proteins whose action is merely added to by the fibrinogen. It appears that the relationship between the variable levels of fibrinogen and the other factors may have some diagnostic significance.

We proposed the term "agglomerin" for all plasma proteins which on the addition of supplement cause an increase in sedimentation rate. In this respect fibrinogen is an agglomerin which is always present in blood. Besides dextran, collodion, and similar supplements, plasma proteins without agglomerin activity may also act as supplements. This can be shown by dividing a

high-sedimenting plasma into two parts, one of which is then diluted with physiological saline, and the other with an AB-serum-citrate mixture (1:5 with 3.8% sodium citrate). In the first case both the agglomerins and supplement are diluted, in the second only the agglomerins. Differences between the two dilutions will then depend on their supplement. Typical results are shown in Fig. 1.

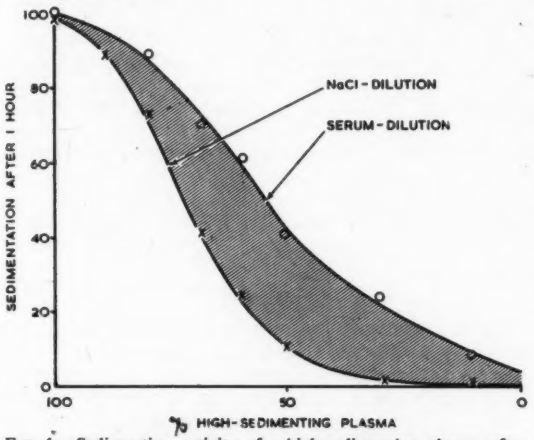

FIG. 1.—Sedimenting activity of a high-sedimenting plasma after dilution with saline or normal serum.

Our investigations have shown that the agglomerins of different patients are not always found in the same electrophoretic fraction. Activity may also be present in two different protein fractions, but serum albumin is always negative (see Table).

Differences in agglomerins can also be shown in another way. There are numerous substances which in a concentration from 0.05 to 0.2% inhibit the sedimentation rate. Although they may be quite different chemically, they exert their effect through binding the agglomerins in a varying degree (Ruhenstroth-Bauer, 1961). They may be classified as complete or partial blocking agents. An example of the former is lauric acid (Formijne, 1956) and of the latter antazolindine (Tange, 1955; Schultheiss *et al.*, 1958). A wide range of blocking activity has been noted for the partial blockers. Slight modification in the structure of salicylic acid leads to a marked change in its blocking activity (Ruhenstroth-Bauer *et al.*, 1960). A given agglomerin is inhibited by partial blockers in a characteristic but variable manner. Typical sedimentation characteristics are noted, and they may be used for the identification of the agglomerin. It has not been determined whether variations in agglomerins are due to individual specificities or to organ specificities or pathologically induced differences.

Normal as well as pathological plasmas contain high molecular lipoproteins which act as pro-inhibitors of sedimentation and which are activated at 37° C. by a specific plasma lipolytic enzyme. The bond between the inhibitor and the red cells appears to be much stronger than that between the agglomerins and the red cells (Ruhenstroth-Bauer, 1957, 1959).

A study by Gross *et al.* (in preparation) on 55 patients has confirmed our observation that the pro-inhibitor–lipolytic system has on the average a lower activity in malignant disease than in inflammatory conditions (Fig. 2).

The true lipases are enzymes which split emulsified fatty esters but not esters which are in true solution (Sarda and Desnuelle, 1958). Enzymes which split fatty esters that are in true solution belong to the esterases which are classified according to substrate and inhibitor specificity. According to its inactivators the

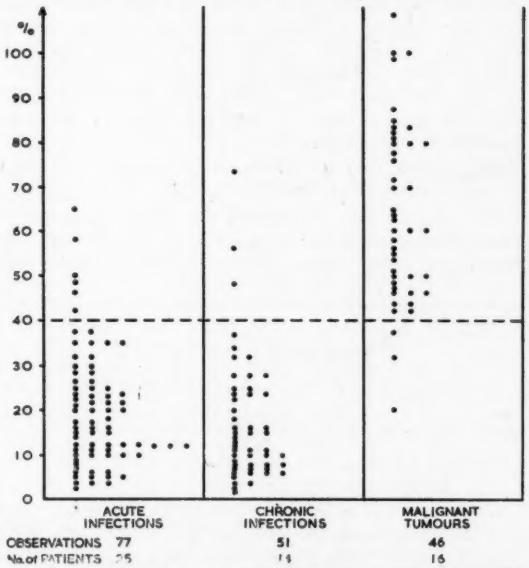

FIG. 2.—Activity of the pro-inhibitor-S-lipase system of different high sedimentation human plasmas (100% = no inhibitor activity).

Sedimenting Activity of Fractions of Proteins of Pathologically Sedimenting Human Plasmas

Plasma Fractions	Sedimentation after Half/1/2/18 Hours in 10 Experiments									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Albumin 5% ..	0·2/0·5/1/14	—	—	—	0·2/1/3/24	0·2/0·5/2/15	—	0·8/2·5/6·5/30	0·3/1/3/12	0·2/1/2/27
Albumin 1·5%	0·2/0·5/1/11	0·5/2 4/21	0·5/1/1/18	0·5/2/4 40	0·2/1/2 15	0·2/0·5/2/12	0·2/0·5/0·5/7	0·5/1·5/4/25	0·5/2/4/15	0/2/4/30
α_1-Globulin 1·5%	0·5/1/3/37	0·2/1 3/18	0·5/1/2/11	0·2/0·8/2/20	0/0/0·2/4	5/10/20/80	0·2/0·5/1/19	60/85/112/120	0·5/1/2/24	2/6/15/69
α_2-Globulin 1·5%	53/104/ 116/124	0·2/0·2/0·8/10	0/0/2/4	0·2/2 6/17	2/10/30/110	28/80/100 120	0·2/0·5/0·8/10	3 16/40/80	3 9/21/104	3/16/35/90
α_2-Globulin 1%	17/38/70/116	—	—	—	—	—	—	—	—	—
β-Globulin 1·5%	0·2/0·5/0·5/5	0/0/1/19	0/0/1/3	0·2/0·2/0·8/5	3/6/15/73	0·2/0·2/0·5/4	0·2/0·8/8/19	0/0/0·5/3	10/20/34/98	0·2/1/2/19
γ-Globulin 2·5%	34/76/85/101	—	—	—	—	—	—	—	—	—
γ-Globulin 1·5%	2·8/24/69	1/2/6/25	10/35/53/87	8/25/45/101	20/52/83/100	2/10/30/53	0·5/1/21/42	0·2/0·5/3/27	0·2/0·5/3/27	0·2/0·5/1/6
Diagnosis	Broncho-pneumonia	Acute nephritis	Chole-cystitis	Hodgkin	Pneumonia	Broncho-pneumonia	Pleuro-pneumonia	Acute polyarthritis	Pancreas Ca (?)	Paramyelo-blastic leukaemia

sedimentation-active lipase belongs to the so-called B group of esterases. One can prepare material from the microsomes of hog pancreas whose effect resembles this enzyme.

Erythrocytes yield a glucolipid fraction which combines with the agglomerins. As little as 50 μg./ml. of plasma of this partially purified material will cause a 50% inhibition of the sedimentation rate (Ruhenstroth-Bauer *et al.*, 1960). Apparently the isolated receptor substances combine with the agglomerins and prevent them from combining with the erythrocytes. The blocking substances would then behave like these isolated receptor substances by competing with the erythrocytes for the agglomerins. Fig. 3 shows a scheme of the proposed mechanism of erythrocyte sedimentation.

A study of the blocking activity of numerous substances has shown that almost all of the anti-inflammatory substances are strong blockers of agglomerins. This applies to salicylic acid (Bendien, Neuberg, and Snapper, 1932), gentisic acid, phenylbutazone (" butazolidin "), " irgapyrin," and cinchophen (" atophan ") (Martin and Scheidegger, 1952), polyphloretin phosphate (Fries, 1959), and the bioflavanoids (Menkin, 1959). Cortisone and resorcinol are partial blockers. Chemically similar substances without anti-inflammatory activity are poor blockers—for example, *o*-oxybenzoic acid shows a very good therapeutic effect and is a good blocker, *m*- and *p*-oxybenzoic acids are inactive in both respects (Formijne, 1955). This suggests that a decrease in agglomerin concentration will result in a decreased inflammatory response.

As regards the mechanism by which agglomerin production is stimulated, we have suggested that material from either homologous or heterologous (bacterial) cells may be the effective agent. Intravenous administration to rabbits of certain fractions separated from different strains of *Escherichia coli* and other bacteria can produce a high sedimentation rate (Ruhenstroth-Bauer *et al.*, 1960). As in the case of man, only a part of the activity is due to an increased fibrinogen level (Ruhenstroth-Bauer *et al.*, 1961). The active fractions of *E. coli* are water-soluble, non-dialysable, and heat-stable (1 hour at 100° C.).

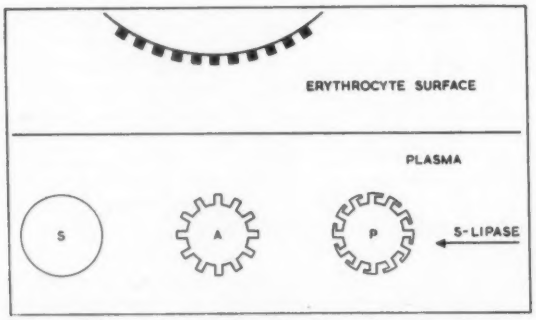

FIG. 3.—Scheme of mechanism of sedimentation of erythrocytes. On the erythrocyte surface are specific receptors for the agglomerins (A) of the plasma. S=Supplement. P=pro-inhibitor which is converted to inhibitor by a specific lipase. On conversion it can compete with the agglomerin for the red-cell surface.

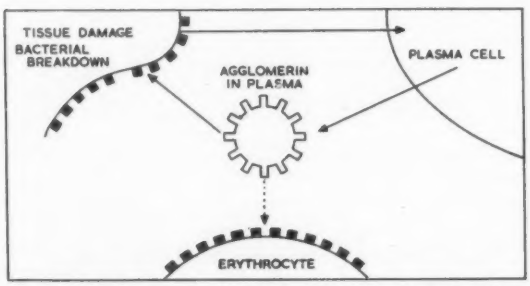

FIG. 4.—Scheme of the biological significance of agglomerins.

It is probable that with the breakdown of cells substances are liberated which can stimulate the formation of agglomerins by plasma cells (Fig. 4). These agglomerins would then be carried by the blood plasma to the damaged area, where their effect is manifested by an inflammatory response. The erythrocytes appear to possess receptors similar to the damaged cells and can therefore likewise combine with agglomerins. The release of different substances from the damaged cells would be expected to account for the different types of agglomerins.

Summary

A high sedimentation rate is caused by specific plasma proteins which are designated agglomerins. They resemble incomplete antibodies in that they require for their expression a high-molecular non-specific supplement. Every plasma contains a pro-inhibitor of sedimentation which is activated at body temperature by means of a specific lipase. A glucolipid fraction can be obtained from erythrocytes that contain the substance which combines with the agglomerins. A concentrate of this receptor substance added to whole blood (50 μg./ml.) decreased the sedimentation rate by 50%. A fraction from *E. coli* will on administration to rabbits produce a high sedimentation rate. Rabbits, like man, then produce agglomerins, of which fibrinogen is only a minor part. Almost all anti-inflammatory substances are inhibitors of agglomerin action. It is suggested that agglomerins are involved in the inflammatory response and that their action on the red cells is only coincidental.

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The National Council of Social Service (Incorporated) has published a booklet on behalf of the National Old People's Council called *The Organization of a Visiting Service*, by an Old People's Welfare Committee. The booklet, recognizing the necessity for a planned visiting service for old people, gives recommendations for organizing such a service which are based on practical experience. There are appendices describing training courses for visitors, and examples of visiting services in various parts of the country; a useful list of publications is included. (From N.C.S.S. (Inc.), 26 Bedford Square, London W.C.1, price 4d.)

Preliminary Communications

Pernicious Anaemia and Gastric Cancer in England and Wales

Attention has recently been drawn to large geographical variations in the incidence of pernicious anaemia in the population of the United Kingdom (Scott, 1960). Wide geographical variation in the mortality rates of cancer of the stomach has also been reported (Stocks, 1958). Since cancer of the stomach is a well-recognized complication of pernicious anaemia (Kaplan and Rigler, 1947; Mosbech and Videbaek, 1950), this small study was undertaken in an attempt to compare the regional distribution of these two diseases in England and Wales.

MATERIALS AND METHODS

Figures of population and of the number of deaths ascribed to pernicious anaemia and subacute combined degeneration of the cord (I.S.C. Nos. 290.0 and 290.1) and to malignant neoplasms of the stomach (I.S.C. No. 151) for the five-year period 1954–8 were obtained from the Registrar-General (1960, personal communication). These figures were subdivided into sex- and age-groups in each of the Registrar-General's 10 standard regions. The constitution of the standard regions is given by the Registrar-General (1960).

For brevity, the two disease groups defined above are here referred to as pernicious anaemia and gastric cancer groups.

Mortality rates of pernicious anaemia and of gastric cancer were calculated for each age-group of each sex for England and Wales as a whole. The number of deaths due to pernicious anaemia and gastric cancer to be expected in each of the 10 regions was calculated by multiplying the appropriate mortality rates for the whole of England and Wales by the population in each age- and sex-group, in each region. The total figures obtained are the expected number of deaths in each region, assuming a uniform mortality rate throughout the country, corrected for regional variations in age and sex composition of the population. The ratio of the expected number of deaths (as calculated above) to the actual number of deaths notified was then expressed as a percentage: this is the comparative mortality figure.

RESULTS

The comparative mortality figures of each of the 10 standard regions of England and Wales, for pernicious anaemia and gastric cancer, are given in the Table.

The areas of highest comparative mortality figures for pernicious anaemia are in the north and west, and the lowest in the south and east (Fig. 1). There is little difference between the comparative mortality figures for males and females ($r=+0.966$) (Fig. 2).

The areas of highest comparative mortality figures for gastric cancer are also in the north and west and the lowest in the south and east (Fig. 3). There is also little difference between male and female comparative mortality figures ($r=+0.926$) (Fig. 4).

Regional variations in the comparative mortality figures for pernicious anaemia are more marked than those for gastric cancer: the highest and lowest being 164% and 56% for pernicious anaemia and 142% and 80% for gastric cancer.

There is a marked positive correlation between the comparative mortality figures for pernicious anaemia and those for gastric cancer ($r=+0.846$) (Fig. 5). This is a significant correlation ($P<0.001$) considerably outside the range of twice the standard deviation of no correlation ($r=0\pm0.459$).

Comparative Mortality Figures for Pernicious Anaemia and Subacute Combined Degeneration of the Spinal Cord and for Malignant Neoplasms of Stomach in the Registrar-General's Standard Regions of England and Wales, 1954–8 (inclusive), Expressed as a Percentage

Region	Sex	Pernicious Anaemia + Subacute Combined Degeneration of Cord		Malignant Neoplasm of Stomach	
		Each Sex Alone	Both Sexes Together	Each Sex Alone	Both Sexes Together
1. Northern	M	123	129	118	123
	F	133		131	
2. E. and W. Ridings	M	135	130	108	109
	F	127		109	
3. North-Western	M	157	174	113	116
	F	182		118	
4. North Midland	M	98	93	92	92
	F	90		91	
5. Midland	M	110	117	100	104
	F	121		108	
6. Eastern	M	70	59	85	85
	F	54		84	
7. London and South-East	M	54	56	90	87
	F	57		83	
8. Southern	M	70	64	81	80
	F	62		78	
9. South-Western	M	94	81	91	90
	F	76		89	
10. Wales	M	152	164	137	142
	F	169		149	

DISCUSSION

The College of General Practitioners' collective investigation has revealed large regional variations in the incidence of pernicious anaemia in Great Britain. The highest rates were in the north and west and the lowest in the south and east. The highest rate was more than twice the lowest (Scott, 1960). The geographical pattern of distribution of pernicious anaemia reported by Scott is very similar to that obtained in the present study. This is of interest, since Scott's figures are derived from the numbers of live patients throughout the country, while the comparative mortality figures used in the present study are derived from the number of deaths ascribed to pernicious anaemia on death certificates. Thus it appears that comparative mortality figures in this instance reflect the geographical trends of a chronic disease among the population.

No data for the variation in incidence of gastric cancer in the live population throughout England and Wales are obtainable, although Stocks (1958) has shown that there is considerable geographical variation in comparative mortality figures for gastric cancer.

The apparent correlation between the comparative mortality figures of pernicious anaemia and of gastric cancer is of interest, for it may imply a common aetiological background to these two conditions. However, it must be stressed that mortality figures may not accurately reflect the true incidence rates in the live population. Further, the geographical regions studied are relatively large, and it is therefore possible that local variations in incidence within the standard regions may be masked. Nevertheless, it is pertinent to consider some of the aetiological factors which may be common to these two conditions.

There are marked familial tendencies in both pernicious anaemia (Stamos, 1940) and gastric cancer (Hagy, 1954). In addition, patients with pernicious anaemia and their relatives have an increased incidence of gastric cancer (Kaplan and Rigler, 1947; Mosbech and Videbaek, 1950).

Both pernicious anaemia and gastric cancer appear to be more common in patients with blood of group A (Aird, Bentall, and Roberts, 1953; Scott, 1960). However, there is a gradient in the frequency of blood group A which is more common in the south than in the north of Britain (Fisher and Taylor, 1940), and is in contrast to the gradients for pernicious anaemia and gastric cancer. It therefore seems improbable that geographical variations in the incidence of pernicious anaemia and gastric cancer can be ascribed to variations in blood group A frequency alone.

Nearly a century ago Haviland (1870) suggested a relationship between geology and variations in the incidence of cancer, and later correlated areas of high cancer incidence with low-lying clay regions and areas of low cancer incidence with high and especially chalk regions (Haviland, 1899). More recently, local variations within an area of high incidence of gastric cancer in North Wales have been intensively studied (Legon, 1951, 1952; Stocks, 1955, 1957). In this area there appears to be a relationship between high incidence of gastric cancer and prolonged domicile on soils which are equable in moisture content throughout the year and which have a high content of organic carbon and high biological activity (Stocks, 1955). In addition, gastric cancer is more common where there is underlying igneous rock and less common where there is underlying chalk or limestone (Stocks, 1957).

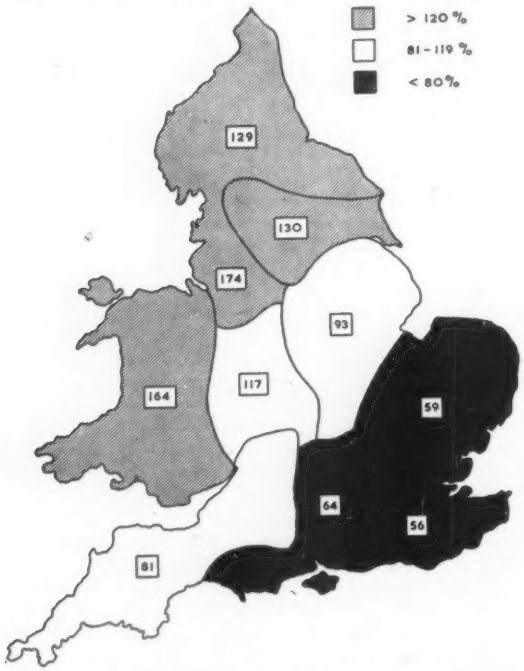

FIG. 1.—Comparative mortality figures (%) for pernicious anaemia in the 10 standard regions of England and Wales (both sexes).

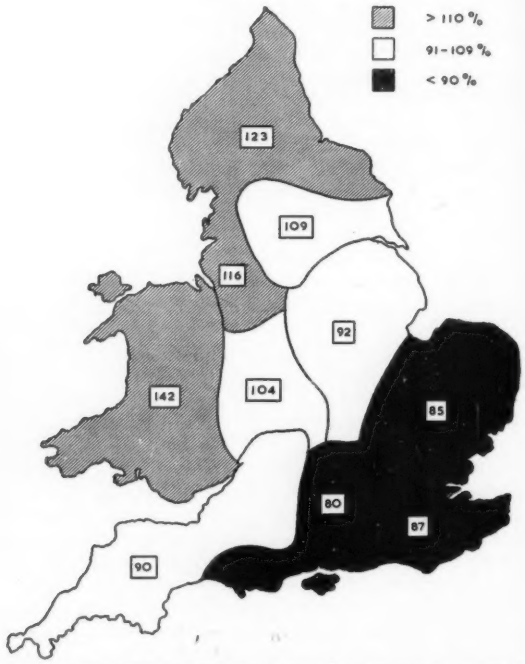

FIG. 3.—Comparative mortality figures (%) for gastric cancer in the 10 standard regions of England and Wales (both sexes).

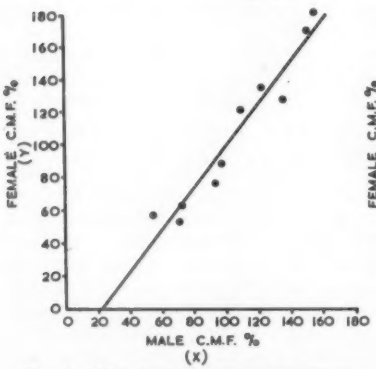

FIG. 2.—Relationship between pernicious anaemia comparative mortality figures (%) in males and females. (Female=1.26. Male=−27.00).

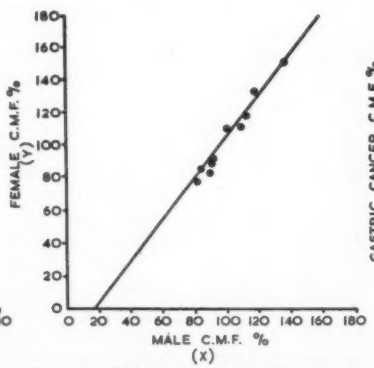

FIG. 4.—Relationship between gastric cancer comparative mortality figures (%) in males and females. (Female=1.24. Male=−20.82.)

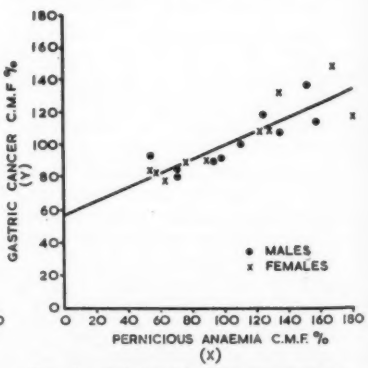

FIG. 5.—Relationship between comparative mortality figures (%) for pernicious anaemia and for gastric cancer. (Both sexes.) (Gastric cancer=0.42. P.A. +57.00.)

It has also been suggested that the incidence of pernicious anaemia can in general be correlated with the underlying geological formation (Scott, 1960). Hargreaves (1960) has noted that the large local variations in the mortality rates of pernicious anaemia in Cornwall may be related to geological structure: areas of high pernicious anaemia mortality are also areas in which "pining" due to cobalt deficiency occurs in sheep. It is possible that these variations may be mediated by differences in source of water supply, for a recent survey has shown that local variations in total cancer mortality in West Devon may be related to areas with different sources of water supply (Allen-Price, 1960). Recently the preliminary results of a survey of natural radioactivity in the water supply of this part of Devon have been published (Abbatt, Lakey, and Mathias, 1960). These results suggest that the natural radioactivity and/or the trace-element content of the water supply may be related to the local variations in cancer mortality in this area.

In conclusion, it is possible to suggest that there may be aetiological factors in these two conditions which are closely related. It is also possible that geographical variation in the supply of trace elements, in particular of cobalt, may be of aetiological importance. Clearly an intensive survey designed to prove or refute such a hypothesis is needed.

SUMMARY

Comparative mortality figures for pernicious anaemia and gastric cancer for the five years 1954–8 of 10 regions of England and Wales are presented.

There is a positive correlation between the comparative mortality figures for pernicious anaemia and for gastric cancer. The north and west of England and Wales have high comparative mortality figures and the south and east low comparative mortality figures for these two conditions.

Various possible aetiological factors are discussed.

I thank the Registrar-General for providing the data on the number of deaths and regional populations and for permission to publish conclusions derived from these data; Drs. J. L. Pinniger and G. Wetherley-Mein for helpful criticism; and Dr. J. L. Pinniger in addition for permission to publish this paper.

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Medical Memoranda

Two Unusual Cases of Torsion of Testicular Appendages

There are four testicular appendages: the pedunculated hydatid of Morgagni, which is present in 90% of normal men, the organ of Giraldès, the vas aberrans of Haller, and the sessile hydatid of Morgagni. These vestigial structures—derived from the paramesonephric or Müllerian duct and the mesonephros—are identifiable by their exact anatomical site and histology.

Torsion of an appendage was first described by Colt (1921–2). Since then approximately 120 cases have been recorded. 106 were torsion of a hydatid, two were torsion of the organ of Giraldès, and one was torsion of a vas aberrans. Only six cases of torsion in association with maldescent of the testis have been described. All six were torsion of the pedunculated hydatid of Morgagni. In three the testis was abdomino-inguinal (Lagos Garcia and Cucullu, 1929, 1930; and Chidichimo, 1940), and there was an associated congenital inguinal hernia (cf. Case 2 below). In two cases the testis was in the inguinal canal (Foucault, 1925; Moncalvi, 1933), and in the sixth case it was at the external ring (Shattock, 1922) and had two gangrenous appendages.

Dix (1931), Randall (1939), and Aird (1957) have written good accounts of this disorder. Bender (1951) noted that, of 97 cases then on record, only 7 had occurred over the age of 20 years. Dix stresses the importance of operation in all cases of suspected torsion of a testicular appendage, in view of the difficulty of excluding a torsion of the testis itself, which has been reported as an associated finding.

If a maldescended testis is intra-abdominal, torsion of its appendages may simulate an acute abdominal condition. If it is inguinal it may resemble torsion of the testis itself, acute epididymo-orchitis, strangulated inguinal hernia, or acute inguinal adenitis.

CASE 1

A boy aged 13 years attended the casualty department on November 9, 1957, complaining of slight pain in the left testicle for a day, worse for the past few hours. There was no history of nausea, vomiting, or trauma, but the father reported that the boy had complained of discomfort on and off for some time. On examination the patient was in obvious pain. His temperature was 99° F. (37.2° C.) and the left side of the scrotum was red, swollen, and extremely tender. Torsion of the left testis was diagnosed. At operation that evening the testicular coverings were oedematous, and within these was a normal testis. There was no free fluid in the tunica, and a plum-coloured appendage was found on a narrow twisted pedicle which was arising from the sulcus between the head of the epididymis and the upper pole of the testis. The appendage was 15 mm. long, bilobed, with the pedicle arising from the junction of the two lobes. It was not sectioned.

Comment.—This was a classical presentation of the condition in almost all respects, but there was no previous record of a bilobed appendix.

CASE 2

A boy aged 15 years was sent to the casualty department by his general practitioner on November 12, 1957, with a suggested diagnosis of appendicitis. There had been pain

in the right iliac fossa for the preceding 24 hours, but this passed off after defaecation before the boy arrived at the hospital. He admitted to twinges of similar but less severe pain at times in the past. There was no fever, the right side of the scrotum was empty, and the testis was not palpable in the inguinal canal. He returned on November 17 with recurrence of the symptoms, especially on lying down, and tenderness to pressure in the right iliac fossa.

On examination no real tenderness was demonstrable and the patient was afebrile. He attended again the same evening because of an aching pain in the right groin. There was marked tenderness over the right inguinal canal, and there was a slight swelling of the right groin compared with the left. There was also a small lump presenting at the internal ring, with a definite cough impulse. His temperature was 99° F. (37.2° C.) and pulse 104 a minute. Subacute torsion of an undescended testis was diagnosed.

At operation a small congenital hernial sac with a wide neck was disclosed, with the right testis emerging into the inguinal canal through the internal ring. The right testis was three-quarters the size of the left but otherwise apparently normal. Arising from the caput of the epididymis was a small pedunculated gangrenous appendage wrapped in omentum. The appendage was excised and orchiopexy performed. Macroscopically the appendage was a dull, plum-coloured ovoid mass, 7 mm. long by 4 mm. wide, which from the site of attachment of its pedicle appeared to be an appendix epididymis. Microscopical examination showed: "A tubular columnar epithelium, rather like that of epididymis but spoiled by autolysis. The outer covering is completely missing, probably for the same reason. It does not resemble the available specimens of torsion of the hydatid of Morgagni, none of which has internal tubules."

Comment.—This case demonstrates the confusion which can occur in diagnosing this condition. Whether the cause of the torsion was the obvious attempt of the testis at descent is a matter for speculation. There seems to be no previous record of torsion of the appendix epididymis associated with maldescent of the testis.

I am indebted to Mr. R. Parkinson and Mr. J. T. Fathi for their permission to publish these cases, and to the latter for encouraging me to do so. I would like to thank Dr. J. W. Landells, of the Bernhard Baron Institute of Pathology, London Hospital, for preparing and commenting on the pathological section.

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A Rare Complication of Twin Delivery

CASE HISTORY

A woman of 47 who had previously had eight full-time pregnancies and one abortion was found to have a twin pregnancy. At the 32nd week she was admitted to hospital for a period of rest as a precaution against very premature labour (Bender, 1952), remaining for over two weeks without untoward signs or symptoms. At the 36th week she developed marked oedema of the legs but no hypertension or albuminuria, and she was readmitted.

At 4.15 a.m. on February 22, 1961, 27 days before her expected date of confinement, there was spontaneous rupture of the membranes and strong contractions followed immediately. The first twin was presenting by the head and the second by the breech. The mother was transferred to the labour ward, where the medical staff were already fully engaged on another complicated delivery. At 5.25 a.m. the cervix was fully dilated and almost at once the head of the first baby appeared at the vulva, but its delivery was found by Sister S. M. Jones, who was perforce conducting the delivery, to be impeded by the umbilical cord being tightly round the baby's neck. The cord was doubly clamped and cut, and the baby, a girl weighing 6 lb. (2,720 g.), was born at 5.30 a.m.—with her cord intact and leading back into the vagina.

Fortunately for this disconcerting train of events, the strong contractions continued. There was no second bag of membranes, and the second foetus, which was presenting as a flexed breech, was spontaneously expelled within five minutes of the first. This girl twin, who weighed 5 lb. 9 oz. (2,525 g.), was a little shocked at birth but soon cried well. Ergometrine 0.5 mg. was given intravenously and the third stage was normal.

The placenta weighed 2 lb. (905 g.) and was uniovular with one chorion and one amniotic sac. There were no knots in either cord. The mother and her identical twin daughters did well and left the hospital in good condition.

COMMENT

Monoamniotic twins have been reported with increasing frequency since the classic paper of Quigley (1935), but, in all, fewer than 200 cases have been described in the literature. Yet when the condition is carefully looked for it is reckoned to be present in from 1 in 165 (Raphael, 1961) to 1 in 65 (Librach and Terrin, 1957) twin deliveries. And as an increasing incidence has been reported, so in an increasing proportion of cases have both babies survived—from the 16% quoted by Quigley (1935) to the 46% calculated by Raphael (1961) for cases reported since 1935. The foetal loss is largely due to interference with the foetal circulation by twisting and knotting of the umbilical cords.

The particular danger which arose in this case—namely, that if the cord not known to be that of the second twin is cut because it impedes the delivery of the first twin then the second baby is in jeopardy unless promptly delivered—has been mentioned as a hazard of monoamniotic twins by several recent authors—for example, Green *et al.* (1960) and Raphael (1961).

Moral.—There is an increasing tendency for immediate delivery of the second twin after the first in *all* cases; in monoamniotic twins it is essential for good foetal results. Whenever after delivery of the first twin no second bag of membranes is found, or its cord is seen to be knotted or twisted, or the "wrong" cord is seen to have been cut, the second baby must be delivered at once.

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The Empire Rheumatism Council has made a grant of £20,000 to establish a unit at King's College Hospital Medical School which will undertake research on the effect of certain well-established drugs on the cells of the body. The unit will be under the direction of Dr. M. J. H. SMITH.

Reviews

ESSENTIALS OF NEUROLOGY

Essentials of Neurology. By John N. Walton, M.D., M.R.C.P. (Pp. 422+xviii; illustrated. 30s.) London: Pitman Medical Publishing Company Limited. 1961.

Textbooks concerned with rapidly advancing branches of medicine are difficult to keep up to date as new editions appear, and on the whole it seems best that every generation should produce a new set of textbooks. The relatively young author of this textbook is to be congratulated on his clear exposition of current knowledge, and it may be strongly recommended to postgraduate students and practitioners. In a search for something to criticize the reviewer finds inadequate information on the treatment of status epilepticus, and it seems regrettable that the techniques of studying the strength of individual muscles are considered to be outside the scope of this book.

In the treatment of the myelopathy associated with cervical spondylosis the use of a collar to restrict weak movements is considered to be "probably of little value," but on the contrary many students of this condition find that improvement or arrest of progress from restricting weak movement is often achieved, and indeed that the improvement which occurs with a collar may provide better information regarding the diagnosis than does myelography.

However, these are small points, and on the whole the book may be praised without reservation.

W. RITCHIE RUSSELL.

INTUSSUSCEPTION

Intussusception in Infants and Children. By Mark M. Ravitch, M.D. (Pp. 121+xi; illustrated. 76s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

This is a well-written monograph by a surgeon with a great experience of his subject. An interesting historical introduction precedes the chapter on the clinical picture of intussusception. The apparent but unexplained infrequency of the condition in the U.S.A. compared with Great Britain is of interest. In his description of the illness the author draws on the literature of Europe as well as that of his own country and his own experience. The natural history of the disease appears to be identical.

A chapter on errors of diagnosis is frank and useful. The confusing type of intussusception which is not obstructed and presents to the physician as "dysentery" is stressed. The opinion that "a sense of urgency in the presence of the possibility of intussusception should reduce the number of diagnostic errors" and that "one should not insist on feeling a mass before resorting to barium enema" is worthy of quotation. As a result of this attitude there have been no deaths from intussusception in the Johns Hopkins Hospital for twelve years.

Pathological and experimental studies are described. The experimental production of intussusception in dogs and their treatment did not seem to the reviewer to contribute much, but the finding of bacterial contamination of the outer surface of completely viable bowel in several cases is interesting.

The author is well known for his championship of primary hydrostatic treatment by barium enema. He presents a convincing case for the safety and efficacy of this method when the pressure is restricted to 3½ ft., the use of abdominal manipulation is rigidly eschewed, and the procedure is under the control of the surgeon from the outset. The case for operative treatment is also fairly put, so that some may feel that there are now two adequate attitudes to treatment. On almost the last page of the book the author cannot resist a biased comment on "the manual squeezing, pulling, and hauling of operative reduction." But he will readily be forgiven this lapse in such a well thought out and presented review of the present position in regard to intussusception.

There are many illustrations, most of which make their points clearly, and the bibliography is excellent.

H. H. NIXON.

TROPICAL PATHOLOGY

Techniques in Tropical Pathology. By B. G. Maegraith, W. E. Kershaw, V.R.D., and D. Dagnall. (Pp. 164+xi. 25s.) Edinburgh and London: Oliver and Boyd. 1961.

This unpretentious little book is intended to supply the isolated practitioner or technician in the tropics with information regarding all procedures likely to be required in a small laboratory, and with instructions on how to collect and send materials to central laboratories. Brief notes are given of certain more complicated techniques used in central laboratories.

In addition to accounts of examination of the materials normally investigated as a routine in temperate climates we find descriptions of protozoa, helminths, snails, and mosquitoes, with methods of collection and dissection. Much-needed warning is given against careless picking of snails by hand from the water.

This book, moderately priced when the excellent colour illustrations are considered, will be found useful by those working for the D.T.M.&H. and for the final examination in parasitology of the Institute of Medical Laboratory Technology.

GEORGE R. MCROBERT.

GYNAECOLOGICAL OPERATIONS

Atlas der Gynäkologischen Operationen. By Professor Dr. O. Käser and Dr. F. A. Iklé. (Pp. 451+viii; illustrated. DM. 148.) Stuttgart: Georg Thieme Verlag. 1960.

The contrast between theoretical and practical training is nowhere more apparent than in operative surgery. Half an hour alone in the abdomen is worth more to the tyro than all the pictures in all the textbooks; there can be no substitute for practical experience. But even those with ample opportunity for acquiring dexterity at the table need more than the direction of their seniors, and this atlas of gynaecological operations will prove the ideal vade-mecum for the younger surgeon. Written by Professor Käser, one of the best-known Swiss teachers, and his assistant, Dr. F. A. Inkle, it is beautifully illustrated by K. H. Seeber, of Tübingen. The collaboration is close and continuous, making reading and observation almost synchronous. Each drawing—and there are over 700—is carefully designed as a schematic illustration of its particular paragraph, with all non-essential "artistry" removed. The result is the clearest and most practical exposition of the whole subject, vividly presented and easily followed.

In a work of this scope it is of course inevitable that some of the methods advocated will not command

universal agreement. The manner of holding the vulsellum during curettage will hardly appeal to the practical gynaecologist, while the illustration showing the delicate pen-like grip on the bougie perpetuates a dangerous and inefficient manœuvre. It is also disappointing to see the continued advocacy of Hegar's bougies—one had assumed they had been generally replaced by the long modern stem-graduated dilator. These, however, are minor matters, and are probably offset by the belated but full acceptance by a Continental surgeon of the Manchester operation as the optimum treatment for prolapse.

The book is produced by Thieme with the superb finish and clarity associated with that firm's publications, and it is hoped that early translation will give the atlas its deservedly wide public in Great Britain.

ALBERT DAVIS.

LIGHT COAGULATION

Light Coagulation. By Gerd Meyer-Schwickerath, M.D. Translated by Stephen M. Drance, M.B., F.R.C.S.(Eng.). (Pp. 114; illustrated. 71s. 6d.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1960.

One of the major advances of ophthalmic surgery within the last decade is the application of the technique of light coagulation to a number of ocular conditions of which the most important is detachment of the retina. The method was introduced by Meyer-Schwickerath, of Bonn, who performed the first operation on a human being in 1949 after three years' experimental work. The surgical technique has now become standardized, aided by an excellent (although expensive) apparatus designed by Dr. Littman, of the Carl Zeiss Company, and is becoming more and more widely used in most countries of the world. It is good, therefore, that the monograph published by Meyer-Schwickerath in 1959 standardizing his now considerable experience should be available in English.

The physical basis of the method is simple: it depends upon the production of a localized destructive burn by a high-pressure xenon lamp, the beam of light from which is accurately focused on the required spot by an optical system. Localization on the fundus is relatively easy and accurate, since the lesion is first sighted through an ophthalmoscope and the coagulating beam substituted for the observing beam of light. In treating retinal detachments the area of the retina around the tear or hole is coagulated as well as the choroid underneath, so that the retinal hole is occluded in the resulting adhesive chorio-retinitis. Not every detachment is suitable for such treatment, which is especially applicable to the closure of holes at the macula or in the posterior segment of the globe which are difficult to reach for coagulation by diathermy, to the limitation of residual post-operative detachments, and as a prophylactic measure in the coagulation of holes or degenerate areas elsewhere in the retina, particularly in the periphery. In addition, light coagulation is an easy way to treat circumscribed lesions such as periphlebitis of the retina, angiomatosis, and—occasionally—early malignant melanomata or neuroblastomata in an only eye. In the iris an artificial pupil may be fashioned and such lesions of the lids as xanthelasma may be destroyed. Sufficient experience has been gathered during the last 10 years to allow a reasonable assessment to be made of the value and limitations of the new technique, which are fairly assessed in this small volume.

STEWART DUKE-ELDER.

PHYSICAL VIEW OF BEHAVIOUR

The Neural Basis of Human Behavior. By Harold Saxton Burr, Ph.D. (Pp. 261+ix; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

This is a disappointing book because it fails to fulfil its declared and stimulating intention. It aims to describe the physical bases of human behaviour, and the claim implicit in its introduction is that it should offer some tentative biological formulation of the problems of interpersonal relations between individuals and between social groups. This it makes little attempt to do. Indeed, it hardly deals with the subject at all, and remains firmly anchored to the anatomical substrate. Even the chapter on the temporal lobe, for example, contains no account of psychopathic personality and behaviour, the anatomical and physiological correlates of which would surely furnish material for a stimulating essay on the nominal subject of the volume.

In fact, it comprises a workmanlike account of the organization of the nervous system, illustrated by a few excellent diagrams and without an index. The reviewer is left in some doubt as to the kind of reader for whom it is intended. The presentation is in simple terms appropriate to a book for the educated laymen. On the other hand, the anatomical detail is considerable, but unlikely to interest any reader without expert knowledge, for whom the book—which contains nothing new—is likely to have little appeal.

The author's few attempts to take off from the well-tilled ground of morphology into the windy skies of generalization and speculation do not excite enthusiasm. His "explanation" of the juvenile delinquent, for example, "whose basic needs of food, shelter, love, and importance never yields [*sic*] to the regulatory impact of neural currents generated in the cortex" lends scant support to his central and highly questionable contention that "the answer to the problem of human behaviour can best be solved by a more adequate knowledge of the structure and function of the nervous system."

This view would not, of course, lack support in Great Britain, where the disproportionate prestige of neurophysiology in the hierarchy of the medical sciences has ensured a favourable reception for some of the most jejune and obscurantist of such exercises in analogy. To the reviewer it seems improbable that the mysteries of human behaviour will reveal themselves more readily to the man whose days are spent in the intriguing company of the Purkinje cell, the eviscerated frog, or the decapitated rabbit, than to one whose experience is with man himself in his social environment. Such doubts are not stilled by a perusal of Dr. Burr's pages.

HENRY MILLER.

PROGRESS IN ENDOCRINOLOGY

Progress in Endocrinology. Part I. *Neuroendocrinology and Endocrinology of the Thyroid and Parathyroid Glands.* (Pp. 165+x; illustrated. 45s.) Part II. *Biochemistry and Biological Actions of Steroids and Other Hormones.* (Pp. 167+xi; illustrated. 45s.) Proceedings of the Edinburgh meeting on Endocrinology, August 16–20, 1959. Edited by K. Fotherby, J. A. Loraine, J. A. Strong, and P. Eckstein. Cambridge: The University Press. 1960.

Current advances in medicine owe much to the cross-fertilization of ideas which takes place at international meetings and symposia. These two volumes (Nos. 9 and 10) of *Memoirs of the Society for Endocrinology* report a congress held in Edinburgh in August, 1959,

under the Presidency of Sir Charles Dodds. It was the first joint meeting between the British Society of Endocrinology and the societies representing the Acta Endocrinologica Congresses.

About two-thirds of the papers reported are included in four symposia. The first three, on "Neuroendocrinology," "Thyroid Gland," and "Parathyroid Glands," make up Volume 9 (Part I). Volume 10 (Part II) includes the fourth symposium entitled "Are the Endocrine Glands directly related to Cancer?", and the remaining papers grouped under the headings "Steroid Biochemistry" and "Biological Actions and Interrelationships of Steroids and other Hormones."

The symposia deal mainly with growing points and give a representative picture of recent European achievements in these sectors of endocrinology. Much of what is presented is new, and some is of rather specialized interest. But for the general or more philosophically minded reader there are many well-balanced reviews of recent work presented by authors as a framework for their own contributions. Out of so many stimulating papers it is perhaps unfair to name but a few. New aspects of the relationships between the hypothalamus and pituitary gland are discussed by such authorities as L. Martini, G. W. Harris, and B. T. Donovan, and G. F. Marrian reviews recent advances in oestrogen biochemistry. Of special interest to the clinician are "The Treatment of Hyperthyroidism," by A. G. Macgregor, "Autoimmunity and the Thyroid Gland," by I. M. Roitt and colleagues, and some of the papers on the endocrine therapy of cancer including medical adrenalectomy. Many of the discussions are included, and, though generally lacking in the racy spontaneity generated by more intimate symposia, these add greatly to the value of the communications.

Each volume is separately indexed and the editors are to be congratulated on the clarity, elegance, and quality of their production, including many excellent tables and illustrations.

OLIVER GARROD.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Freud and the Post-Freudians. By J. A. C. Brown. (Pp. 225 +viii. 3s. 6d.) London: Penguin Books. 1961.

Common Diseases of the Ear, Nose and Throat. By Philip Reading, M.S.(Lond.), F.R.C.S.(Eng.). Third edition. (Pp. 264 +viii; illustrated. 24s.) London: J. and A. Churchill Ltd. 1961.

An Approach to Community Mental Health. By Gerald Caplan, M.D., D.P.M. (Pp. 262+ix. 25s.) London: Tavistock Publications. 1961.

Progress in Clinical Medicine. By various authors. Edited by Raymond Daley, M.A., M.D.Cantab., F.R.C.P., and Henry Miller, M.D.Durh., F.R.C.P., D.P.M. Fourth edition. (Pp. 345 +x; illustrated. 50s.) London: J. and A. Churchill Ltd. 1961.

Clinical Endocrinology. For Practitioners and Students. By Laurence Martin, M.D.(Camb.), F.R.C.P.(Lond.). Third edition. (Pp. 275+vii; illustrated. 28s.) London: J. and A. Churchill Ltd. 1961.

Virus Meningo-Encephalitis. In honour of Professor K. Todorovic. Ciba Foundation Study Group No. 7. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Margaret P. Cameron, M.A. (Pp. 120+ viii. 12s. 6d.) London: J. and A. Churchill Ltd. 1961.

Animal Parasites in Man. By N. H. Swellengrebel, Ph.D., M.D., and M. M. Sterman, M.D. (Pp. 652+x: illustrated. 67s. 6d.) Toronto, New York, London: D. Van Nostrand Company, Inc. 1961.

The Medical Register 1961. Parts 1 and 2. (Pp. 3,111+xxiv.) London: The General Medical Council, 44 Hallam Street, W.1. 1961.

A Prelude to Medical History. By Félix Martí-Ibáñez, M.D. (Pp. 253+xix. $5.75.) New York: MD Publications, Inc. 1961.

The Management of Pediatric Practice. By Hugh C. Thompson, M.D., and Joseph B. Seagle, M.S., M.D. (Pp. 172+xv; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Parents of the Handicapped. Self-Organized Parents' and Relatives' Groups for Treatment of Ill and Handicapped Children. By Alfred H. Katz, D.S.W. (Pp. 155+ix. 48s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Thought Reform and the Psychology of Totalism. A Study of "Brainwashing" in China. By Robert Lifton, M.D. (Pp. 510 +x. 30s.) London: Victor Gollancz Ltd. 1961.

Die Gaumenmandel. Darstellung der Biologie und Physiopathologie. By Doz. Dr. Alessandro Fioretti. (Pp. 202+viii; illustrated. DM. 39.80.) Stuttgart: Georg Thieme Verlag. 1961.

Shaw's Summary of Procedural Requirements in Respect of Compulsory Admission to Hospital and Guardianship. Mental Health Act, 1959. (2s. 6d.) London: Shaw and Sons Ltd 1961.

Symptom Diagnosis. By Wallace Mason Yater, A.B., M.D., M.S.(in Med.), F.A.C.P., and William Francis Oliver, B.S., M.D., F.A.C.P. Fifth edition. (Pp. 1,035+x. $15.) New York: Appleton-Century-Crofts, Inc. 1961.

The Integrative Action of the Nervous System. By Sir Charles Sherrington. (Pp. 413+xx. 16s.) Paperback edition. New Haven: Yale University Press. London: Oxford University Press. 1961.

Frustration and Aggression. By John Dollard, Neal E. Miller, Leonard W. Doob, O. H. Mowrer, Robert R. Sears. (Pp. 209. 10s.) New Haven: Yale University Press. London: Oxford University Press 1961.

Family Planning and Modern Problems. A Catholic Analysis. By Stanislas de Lestapis, S.J. (Pp. 326+xx. 30s.) London: Burns and Oates. 1961.

Antikoagulantien in der Humanmedizin. III. Hamburger Sympodion über Blutgerinnung. 28 Mai 1960. Edited by Professor Dr. L. Zukschwerdt and Priv.-Doz. H. A. Thies. (Pp. 166. DM. 19.75.) Stuttgart: Friedrich-Karl Schattauer-Verlag. 1961.

Clinics in Electrocardiography. By Dale Groom, A.B., M.D., M.S.(in Med.), F.A.C.P. (Pp. 152+x; illustrated. 64s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Fetal Electrocardiography. The Electrical Activity of the Fetal Heart. By Saul David Larks, B.S.E.E., M.S.(E.E.), Ph.D. (Pp. 109+xiii; illustrated. 52s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Radiopaque Diagnostic Agents. By Peter K. Knoefel, M.D. (Pp. 157+ix; illustrated. 54s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Biological Approaches to Cancer Chemotherapy. By R. J. C. Harris. A symposium held at Louvain, June, 1960, under the auspices of Unesco and the World Health Organization. (Pp. 431 +x. 96s.) London, New York: Academic Press. 1961.

Arithmetic Review and Drug Therapy for Practical Nurses. By Grace E. Fitch, R.N., B.S. (Pp. 164+viii. 24s. 6d.) New York: The Macmillan Company. 1961.

Exceptional Children. Residential Treatment of Emotionally Disturbed Boys at Shotton Hall. By F. G. Lennhoff. (Pp. 201. 21s.) London: George Allen and Unwin Ltd. 1961.

Symposium on Water and Electrolyte Metabolism, Amsterdam, 1960. Organized by the Netherlands Society of Clinical Chemistry and the Netherlands Society for General Pathology. Edited by C. P. Stewart and Th. Strengers. (Pp. 202; illustrated. 38s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. 1961.

Human Behaviour. A New Approach. By Claire Russell and W. M. S. Russell. (Pp. 532+ix. 42s.) London: Andre Deutsch Ltd. 1961.

Mental Health Services. By Arthur Hubert Edwards, D.P.A. Third edition. Third edition. (Pp. 742+xxxv. 95s.) London: Shaw and Sons Ltd 1961.

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RESPIRATORY SYNCYTIAL VIRUS

When studying an outbreak of coryza in a colony of chimpanzees, J. A. Morris, R. E. Blount, and R. E. Savage[1] recovered a virus which caused syncytia to appear in tissue cultures and which reproduced the disease when inoculated into more chimpanzees. R. Chanock and his colleagues[2 3] subsequently recovered the same virus from children in Baltimore and found some evidence that infection with it was associated with pneumonia. They named the infecting organism respiratory syncytial virus. Their results were indecisive for two main reasons. One was that they isolated the virus only twice. The other was that the results of serological studies on control and ill children showed a high incidence of infection in the "normal" control children, probably because the virus was spreading round the hospital ward. Much more work has been done since then, and it has now been shown that respiratory syncytial virus is an important cause of respiratory disease in man.

In the first place M. Beem and others[4] showed that during an epidemic the virus could be isolated from 50% of children with bronchiolitis, provided the tissue cultures were inoculated with fresh unfrozen material. The proportion of children with minor respiratory disease from whom virus was recovered was less than half, but it was more than the proportion of children without respiratory disease from whom it could be obtained. Now two groups of workers in the U.S.A. have published large clinical studies on the effects of this virus. Chanock and colleagues,[5-8] of Washington, D.C., report that between March and July, 1960, and between November, 1960, and February, 1961 (periods when respiratory syncytial virus was active in the community), they isolated 149 strains from 867 patients with respiratory disease and 5 from 499 control subjects. The virus was obtained from about a third of the patients with bronchiolitis, a fifth of the patients with pneumonia, and from a much smaller proportion of the patients with minor respiratory disease. Between the epidemic periods the virus virtually disappeared. A serological study of 1,590 patients led to similar conclusions, but it appeared that antibody responses were often poor in young children and that infection occurred in subjects possessing antibody. This group of workers gave virus (passed twice in tissue culture) as a nasal and throat spray and as drops to 41 volunteers living in isolation; all these subjects possessed antibody. Virus infection was detected in 19 out of 20 volunteers who developed a cold-like illness and in 14 out of 21 who remained well. Among volunteers who received control inoculum which did not contain virus, one got a cold but none were infected with the respiratory syncytial virus. The level of antibody did not rise in some patients during infection with this virus. Unfortunately the inoculum used contained a simian virus, SV_{40}, and this infected some volunteers, but there was evidence that it had not vitiated the results.

Laurella McClelland and colleagues,[9 10] of West Point and Philadelphia, report on 667 cases of acute respiratory illness and 153 control cases of non-respiratory illness in children under 10. In the group with respiratory illness the new virus caused the disease in 115 cases (17%); in the control group 3 patients (2%) gave positive serodiagnostic results. The disease appeared to run an epidemic course. These workers found that the commonest signs and symptoms of infection with respiratory syncytial virus were rhinitis, cough, fever, and malaise. In about half the cases there was also bronchitis, bronchiolitis, or bronchopneumonia. Pharyngitis and conjunctivitis were rare. The syndrome "could well have been mistaken for epidemic influenza," though the onset of influenza was considered to be usually more abrupt, the rhinitis not so severe, and symptoms from infection of the lower respiratory tract usually not so frequent. Respiratory syncytial virus has also been isolated from adults with minor respiratory illness.[11]

It therefore seems certain that in the U.S.A. respiratory syncytial virus is an important cause of bronchiolitis and bronchopneumonia of children and may cause milder disease in adults. The same is probably true in Great Britain, and information on that is awaited with interest.

[1] Morris, J. A., Blount, R. E., Jr., and Savage, R. E., *Proc. Soc. exp. Biol. (N.Y.)*, 1956, **92**, 544.
[2] Chanock, R., Roizman, B., and Myers, R., *Amer. J. Hyg.*, 1957, **66**, 281.
[3] —— and Finberg, L., ibid., 1957, **66**, 291.
[4] Beem, M., Wright, F. H., Hamre, D., Egerer, R., and Oehme, M., *New Engl. J. Med.*, 1960, **263**, 523.
[5] Chanock, R. M., *et al.*, *J. Amer. med. Ass.*, 1961, **176**, 647.
[6] Parrott, R. H., *et al.*, ibid., 1961, **176**, 653.
[7] Kravetz, H. M., *et al.*, ibid., 1961, **176**, 657.
[8] Johnson, K. M., *et al.*, ibid., 1961, **176**, 663.
[9] McClelland, L., *et al.*, *New Engl. J. Med.*, 1961, **264**, 1169.
[10] Reilly, C. M., ibid., 1961, **264**, 1176.
[11] Hamre, D., Lashof, J. C., Marshall, J. A., Cassidy, J. E., Smith, M., and Bennett, C. R., *Amer. Rev. resp. Dis.*, 1961, **83**, 38.

LEUCOTOMY TWENTY YEARS ON

Though Moniz had reported the experimental use of leucotomy in cases of chronic mental illness as early as 1936, it was not until 1941 that British workers, following the lead of W. Freeman and J. W. Watts in the U.S.A., started to use this method of treatment.

Tremendous feelings were aroused by what was deemed by some to be a surgical assault on the very soul of man, and as late as 1952 a leading article in the *B.M.J.*[1] suggested to worried correspondents that, "if the soul can survive death, it can surely survive leucotomy." Russia banned the operation in 1947, and still does so in all her mental hospitals, because it supposedly conflicts with Pavlovian theory and practice; and the strong influence of Freudian theory in the U.S.A. has also proved an effectual damper to its full use among the enormous numbers of the chronically insane confined in mental hospitals there.

Now, after a long period of checking and rechecking of the statistics, because of the surprising results that have ensued from this inquiry, the Ministry of Health has issued a long-awaited report by G. C. Tooth and Mary P. Newton[2] on the findings in no fewer than 10,365 persons who had a leucotomy operation in mental hospitals in England and Wales between 1942 and the end of 1954. The tracing and grading of these patients lasted from May, 1956, to December, 1957, and most of the rest of the time has been spent in analysing and checking the data obtained. This is by no means a complete survey of all persons subjected to leucotomy in this country during those years, but it is thought to be a good sample of them.

The report shows that 46% of all patients could eventually be discharged from mental hospitals after operation, and 36% of the men and 44% of the women were reported as at least greatly improved after it. These results occurred despite the fact that only 12% of the patients had had the operation within two years of the onset of their illness; as many as 41% had been ill for more than six years before leucotomy was finally used, and their chance of help by other methods was small indeed at that time. In addition to all those able to be discharged from mental hospitals, many more were able to be moved to better wards and to enjoy at least some measure of relief from what has been suggested as the most important indication for leucotomy—namely, a state of "tortured self-concern." Only 2% of both men and women are reported as being made worse by the operation; 4% died directly or indirectly from its effects; and severe undesirable side-effects of leucotomy were reported in 3.1% of the patients, occurring most commonly, as expected, in those over the age of 55. The state of 25% of the patients was regarded as unchanged. In more carefully selected groups of patients, especially those showing prolonged severe depressive and tension states, this report again confirms an oft-repeated finding that much higher percentages of improvement and discharge, in the region of 70%, can be confidently predicted even when all other methods of treatment have failed to help the patient.

There is evidence that the use of the tranquillizers has diminished the need for leucotomy, though the best results in some cases seem to be obtained when leucotomy is supplemented by giving tranquillizers afterwards, especially when the tranquillizers used alone have been unable to get the patient well enough to leave hospital. Sometimes these drugs may muffle the demands for help coming from chronic patients, rather than enable them to get out of hospital and back to work again. We are not likely to see in the future the old full operative cuts used in so many of these patients. Such procedures will be confined only to a few carefully selected patients operated on a second time after the failure of a first more modified "open" or "closed" operation. Newer modified operations seem best when confined to the medial quadrants of the frontal lobes and, whenever possible, to a thorough section of the lower medial quadrants only. Walpole Lewin[3] has recently suggested that surgery should be directed to the orbital cortex for symptoms of anxiety and depression and to the cingulate gyrus for aggression and obsessional disorder.

From 101 operations performed in 1942 the number rose to over a thousand in each year between 1948 and 1954, and it is likely that a few hundred more a year slipped through the follow-up net. The numbers operated on since then have dropped, owing in part to the fact that the back-log of severely agitated patients in so many mental hospitals had at last been treated. And it is unlikely that the number will ever rise so high again with the discovery of other physical methods of treatment which carry with them fewer risks and possible deficits.

[1] *Brit. med. J.*, 1952, **1**, 909.
[2] Tooth, G. C., and Newton, M. P., *Leucotomy in England and Wales 1942-1954*, Ministry of Health, 1961, H.M.S.O. (2s. 6d. net.)
[3] Lewin, W., *J. Neurol. Neurosurg. Psychiat.*, 1961, **24**, 37.

DRUGS AND THE STUDENT

The British Medical Students' Association has made an important contribution to the teaching of pharmacology, therapeutics, and pharmacy.[1] It authorized an investigation into this in February last year, and the report now prepared by Mr. Iain M. Maclean should be studied carefully by all those responsible for teaching these subjects in the medical schools of Britain. The report is based upon replies from twenty medical schools—nine in London, three in the Midland Region, four in the Northern Region,

[1] *Report on the Teaching of Pharmacology, Therapeutics, and Pharmacy in British Medical Schools.* British Medical Students' Association.

and four in Scotland. Two tables at the end give such details as the number of lectures, tutorials, and practical courses, the extent of the course and its position in the curriculum, and the chairs and types of chairs in the subjects. Among these 20 schools there are five chairs of pharmacology, seven combining pharmacology and therapeutics, and one separate chair in therapeutics; in five there is no chair in either subject. In six of the schools there are no tutorials in either pharmacology, therapeutics, or pharmacy. With the exception of the London hospitals, pharmacology is taught as part of the introductory clinical course.

These are just some of the facts carefully compiled and clearly set out. But it is the opinions of the students themselves which are of special interest, providing the basis for the recommendations at the end of the report. Just over half of those who replied thought that their lecture courses "were on the whole quite adequate." About a quarter wanted more lectures on therapeutics, and many wanted to have lectures on this "delivered by a clinician and not by a medical school 'theorist.'" Lectures, of course, came in for criticism, especially in relation to pharmacology, and the opinion is expressed that here "the textbook was a better source of information." A number of those who replied suggested that the real advantage of the lecture was that it provided information on new drugs not mentioned in textbooks, and in this context mention was made of the value of stencilled sheets of notes distributed at the end of a lecture.

Evidently students are critical of their lecturers, a criticism resulting in the first recommendation—namely, "that all teaching staff should have a pedagogical training." Where an appointment on the staff of a school involves research, lecturing, and clinical work, then, the students suggest, ability to teach should be the prime consideration. Throughout the report there is stress on the value of tutorial discussions in small groups of not more than ten students. Pharmacology is described as "a dry factual subject." Some 20% of those who replied said they had never seen an animal demonstration in the pharmacological course; another 20% thought such demonstrations of little value. The predominant view is that there is little or no correlation between theoretical and clinical teaching: "Many were quite bitter about the amount of purely academic and historical material they had to listen to in the pharmacology course, which could have no possible clinical application." The complaint comes from London that the pharmacology course is too far removed from clinical work. From the provinces comes the complaint that there is repetition of physiology during the course on pharmacology. The suggestion is made that the physiology course should be extended into the clinical years and incorporate pharmacology—a plea, in other words, for integration. The report comes down in favour of students testing drugs on themselves. Instruction in pharmacy is regarded as a complete waste of time: some suggested this was a relic of bygone days and others that it was "a token gesture to comply with some G.M.C. regulation." Along with the condemnation of pharmacy comes an equally emphatic one of the Imperial system of measurement, and the suggestion that in its place the metric system should be installed.

The students want above all far more instruction in therapeutics, and preference is expressed for therapeutic ward rounds or clinical pharmacological conferences. They feel that in the systematic lectures on pharmacology not enough emphasis is laid on the commonly used drugs, and that what they regard as this lack of realism would be avoided if therapeutics were more often taught by clinicians. It is of particular interest to note the stress laid upon statistics and ethics. A recommendation is made for lectures on these: "We feel that it is of the greatest importance that he [the general practitioner] should have a basic knowledge of just how a good drug trial should be conducted, so that he may be able to criticize competently the relevant literature which appears in the current medical journals." And the comment is made that new drugs appear on the market with little in the way of proof of the claims made for them. The recommendation for lectures on statistics is coupled with one for lectures on the ethics of conducting therapeutic trials.

Much of what is advocated in the B.M.S.A. report is no doubt acted on in this medical school or another, but the tables show quite a wide variation in the time given to different subjects, their location in the curriculum, and the importance attached to them. No medical school can afford to neglect this highly intelligent report of the B.M.S.A., with its explicit message that as the practitioners of to-morrow the medical students of to-day want to be provided with such a training in medicinal therapeutics that they may use drugs intelligently and with scientific scepticism.

NEW TOWNS FOR OLD

Urban redevelopment raises complicated social problems. The congested centres of our large cities conceal old property which is often heavily overcrowded and needs to be swept away. Much has, in fact, recently been demolished, leaving questions of how best to use the area cleared and how to rehouse tenants displaced

from the old warrens. In the early days of slum clearance there was a tendency to demolish, and leave it at that. If the ground thus cleared was not snapped up for commercial or industrial development or used to further the growth of public utilities it was valuable as breathing space The railway boom, for instance, provided an impetus to slum clearance, but the re-housing of displaced tenants received little or no attention. They were left to fend for themselves and usually became lodgers in near-by houses, which in turn became even more overcrowded. These properties were often very little better structurally than the ones which had been cleared away. The housing of the poorer classes was no longer an attractive proposition to private enterprise, and even when State money became available after the first world war the rehousing of slum dwellers was greatly handicapped by the fact that it was usually possible to rehouse on the same site only a fraction of those who had found cover in the old overcrowded dens. The remainder had to be found other accommodation which was frequently in new local authority housing schemes on the periphery of the city or in flats in high buildings on the old site. Building to great height is beset with serious health and social problems and is not successful unless there is careful selection of tenants with good standards of citizenship and conduct.

Sir J. B. Russell,[1] medical officer of health for Glasgow towards the end of the last century, was deeply interested in the uninhabitable houses of the city and the people who lived in them. Many were nomadic, but there were instances of tenants who had remained for 20, 30, even 40 years. His considered opinion was that, in the main, the people living there were the debris of the city, "the chips and dishonoured stones which fall from the social structure and litter its base." The unfailing answer of the residue of respectable people who continued to live in these surroundings was that they had no intercourse with their neighbours; but that was not wholly possible, and the friendship of such neighbours could be almost as objectionable as their enmity. In Liverpool, C. Vereker, J. B. Mays, and their co-workers[2] have recently been working in the old, dilapidated Crown Street district of the city and have published a report on the social structure and family life of this decayed area against the background of its economic and living conditions. They have found that 60% of the occupied heads of families living in the district worked in inner Liverpool and were discouraged from moving away to outlying areas by good transport facilities and a desire to remain near their place of employment. Families tended to remain rooted to the districts; 40% of those interviewed had brothers and sisters near at hand. Three-quarters of all the houses needed repair or demolition, but decay was patchy. The parts where property was in worse physical shape proved to be socially less disturbed than the others, and to harbour a comparatively stable community; yet it was these physically blighted parts which appeared to stimulate greatest desire to move. The city wards which had proved most stable in the past contained the highest proportion of people expressing a desire to move now. The warm contacts arising from intimate social groups, and from the extended family in particular, are clearly regarded by many as of less importance than opportunity to experience the advantages of better physical and social conditions. In the Crown Street district contacts with social organizations were few; only 9% of children belonged to youth organizations. Less than 3% of the total school population of the areas were attending grammar schools or technical schools.

In the past much rehousing has been uninspired. Too often tenants have been moved from central slums to new housing areas far from friends and with scarcely the most primitive essentials for community life. It is not surprising that some do not take kindly to their new environment, despite the relative grandeur of their houses. It is not easy, when framing redevelopment policy, to balance conflicting claims. In a changing world some degree of sacrifice may be necessary from both planners and planned. Balance requires that two different and equally desirable aims should be secured more or less simultaneously—the provision of adequate physical conditions, on the one hand, and the maintenance of social connexions and family relationships on the other. Vereker and Mays make a plea for closer co-operation between social investigators and planners of urban redevelopment, believing that to spend all our civic resources in the creation of new housing estates to the neglect of the deteriorated inner urban districts is to create social problems for the future which may be as serious as those posed by the slums of the past.

[1] Russell, J. B., *Sociological Aspects of Sanitation*, 1888, reprinted, Roy. San. Ass., Scotland, 1933.
[2] Vereker, C., and Mays, J. B., *Urban Redevelopment and Social Change*. Liverpool University Press. Social Res. Series. Pp. 150. 25s.

EXPORT OF UNIVERSITIES

At a time when relations between Western countries and those of Africa are in a delicate state, but are certainly responsive to helpful advice and policies, Sir Eric Ashby has had some pertinent words to say on universities in the tropical parts of the African continent. Addressing the Manchester Medical Society on May 31, he pointed out that the university, by a process of natural selection working among various types of institutions for higher education, had survived and taken root all over the modern world. Yet other analogous institutions had not succeeded in doing this: he instanced the Islamic madrasa and the Japanese daigaku, which had not adapted themselves to modern conditions. The "export" of universities to under-developed countries was his main theme, together with the adaptation of them to societies which are not in the main stream of European problems.

Societies in tropical Africa, he said, responded to Western education in three successive phases. At first, the European was supremely confident that what he brought was "right" for Africans, whereas Africans were suspicious and hostile. Then Africans adopted unquestioningly the European pattern of education (as an instrument to achieve national aspirations) and were suspicious when Europeans proposed any adaptation to suit African conditions. The third phase (just beginning

in West Africa) was one in which Africans desired to turn Western education from being an alien implantation into something which was adapted and appropriate to African society.

In thinking about the adaptations which might occur as universities took root in Africa, we needed, he said, to affirm one principle and to make three assumptions. The principle was that there could be no compromise about standards in university education; higher education was an international currency, and if a country wanted a university it must be willing to maintain it on the gold standard of learning. The three assumptions to be made about a university in a tropical African country were as follows. First, that its purpose was to change, not to preserve, the indigenous culture. Secondly, its aim was not at first to be supra-national and cosmopolitan, but national, regional, even tribal. Thirdly, higher education must develop at a pace far greater than the pace at which it developed in Europe. The consequences, for the university as an institution, of this principle and these assumptions needed very careful and prolonged study.

GOUT AND SECONDARY POLYCYTHAEMIA

Recent reports have drawn attention to the association of gout and secondary polycythaemia due either to congenital cyanotic heart disease or to respiratory insufficiency.[1-4] Occasional cases of gout in polycythaemic congenital heart disease have been noted before,[5 6] but the association had not been systematically investigated. Gout has been observed among mountain-dwelling Creoles in the Andes with physiological polycythaemia,[7] but racial factors such as those that determine the high incidence of gout in Maoris[8] may be more important there. J. Somerville's study[1] of cases with congenital heart disease leaves little doubt that the association between gout and secondary polycythaemia is more than can be explained by chance alone. Her nine patients, all adults, were found among 400 patients, mainly children, with secondary polycythaemia due to this condition. Even without adjusting for age this is a prevalence of 1 in 50, which rises to about 1 in 20 when adults only are considered. In comparison, J. H. Kellgren, J. S. Lawrence, and J. Aitken-Swan's estimate for the prevalence of gout in adult men,[9] based on a population sample, was 3 per 1,000. In 57 of Somerville's adult patients there was a loose positive correlation between haemoglobin and urate levels in the circulating blood, and all but one of the patients with gout had a haemoglobin concentration of 140% or more, while 7 of them had urate tophi. J. G. Lewis, approaching the problem in a slightly different way, reported 7,500 haemoglobin estimations amongst patients attending a hospital for chest and heart diseases, and discovered that of the 90 patients with a haemoglobin level of more than 120% 4 had gout. The serum urate was estimated in 20 adults in this group and found to be raised in 7 of them. J. G. Lewis and J. E. Gardner, surveying what appears to be much the same group of patients, found a significant correlation between the concentrations of haemoglobin and serum urate.

Thus there seems little doubt that hyperuricaemia is a complication of secondary polycythaemia in adults, and that in some of them it will lead to acute gouty arthritis and formation of tophi. The mechanism is probably the same as that which leads to hyperuricaemia and gout in many other blood diseases and in exfoliative psoriasis, and is related to the increased rate of turnover of nucleic acids. This association has both practical and theoretical implications: practical because chlorothiazide and its derivatives, frequently used to help when congestive cardiac failure develops, increase hyperuricaemia by blocking excretion of urate.[10] Luckily this effect is readily overcome by relatively small doses of salicylates.[11] The theoretical implication is that perhaps we should revise our ideas of the normal levels of serum urate, and should restate them in terms of the patient's normal haemoglobin level. It is already accepted that both serum-urate and haemoglobin concentrations are higher in men than in women. There was no family history of gout in Somerville's or Lewis's cases, so that it is difficult to invoke an underlying gouty diathesis. Rather one must assume that gouty arthritis, by some mysterious consequence as yet not understood, may appear sooner or later in anyone in whom the serum urate is raised high enough for long enough, irrespective of whether the hyperuricaemia is inherited or secondary to other disease.

[1] Somerville, J., *Brit. Heart J.*, 1961, **23**, 31.
[2] Lewis, J. G., *Brit. med. J.*, 1961, **1**, 24.
[3] Cameron, E. A., ibid., 1961, **1**, 34.
[4] Lewis, J. G., and Gardner, J. E., *J. clin. Path.*, 1960, **13**, 502.
[5] Gutman, A. B., *Ann. intern. Med.*, 1953, **39**, 1062.
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[7] Loewy, A., and Wittkower, E., *The Pathology of High Altitude Climate*, 1937, Oxford University Press, London.
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SUBACUTE SPONGIFORM ENCEPHALOPATHY

In 1954 D. P. Jones and S. Nevin[1] described their findings in two patients, aged 66 and 62 years, who died in three to four months from a disease characterized by progressive mental deterioration, focal electroencephalographic disturbances, hemiplegia, and myoclonic epilepsy. Since that report Nevin and colleagues[2] have been able to study the clinical and pathological features of a further six similar cases. They have now given an excellently detailed record of each of these cases, and this will serve as a valuable reference standard for cases of similar or allied conditions encountered in the future. From a critical study of the literature they conclude that 23 cases have so far been reported under different titles. This includes those cases described by H. Jakob and colleagues[3] as subacute presenile spongiform cerebral atrophy. Jakob considers that the morphological characteristics of the disease separate it from pseudosclerosis (Creutzfeldt–Jakob disease), and Nevin and colleagues strongly support this conclusion. They state

that the distribution of cortical changes in pseudosclerosis is different, and that the involvement of the brain stem and the spinal cord motor neurones, together with the primary degeneration of the myelinated tracts, which are both features characteristic of the Creutzfeldt–Jakob disease, are lacking in subacute spongiform encephalopathy. They also believe that the form and extent of status spongiosus in this newly identified disease are peculiar to it. Spongiform change in the cortex, while extending through all its layers, may be restricted to only one side of a cortical fissure. This is one of several morphological features supporting their view that the disease is due to vascular dysfunction.

Though no structural changes were found in the vessels adequate to impair blood flow and to explain vascular dysfunction, there were concomitant vascular disorders elsewhere in the body in 11 out of the 23 cases. The ages of the subjects suggested a vascular degenerative factor; thus, in the eight cases described by Nevin and colleagues only one patient was under 50 years of age. Another patient in the series was a man of 80 years who was dying of a *left* carotid thrombosis and in whom the specific changes occurred in the *right* hemisphere. It is stressed that such local vascular lesions as were present in the cortex were insufficient to account for the characteristic rapidity of the changes, for the whole course of the disease ran only about three months in four of the eight cases and in all of them death occurred in less than two years. It was perhaps significant that four out of the eight cases had a history of previous damage to the brain (perhaps more specifically limited to the cortex). One patient had suffered a fall and the other three had surgical craniotomy for meningioma, abscess, and leucotomy. However, the pathological changes of the spongiform disease were not those of any recognized to be post-traumatic.

If spongiform cerebral atrophy is a degenerative disease, it is in a class by itself and is unrelated to other known degenerations of the central nervous system. As is the case with Creutzfeldt–Jakob disease, Alzheimer's disease, and Pick's disease, the aetiology is unknown. There has been no evidence of any metabolic disorder associated with the disease. Because of the status spongiosus the glial reaction in the cortex is of considerable interest histologically, and J. M. Foley and D. Denny-Brown[4] have postulated that this is due to a primary degenerative process affecting the protoplasmic astroglia. However, Nevin and colleagues affirm that the microglial and astrocyte changes seen are consistent with a purely secondary reaction. But, in view of the propensity of tumour astrocytes to cause microcystic liquefaction in astrocytomas (an effect not obviously vascular), and of their proteolytic properties *in vitro*, it is just possible there may be a connexion between the spongiform liquefaction and the glia in this condition. In some way this may reflect vascular dysfunction. It is clear from other specific disease processes in the brain that vascular dysfunction can declare itself in manifold ways. Brain tissue seems to respond differently to, and to distinguish between, anoxia, anaemia, and ischaemia; and, as in vasospastic sequelae, the time factor related to each of these factors is crucial where selective structural effects are at issue. There is surely much work to be done by an experimental neuropathologist in this field.

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[3] Jakob, H., Eicke, W., and Orthner, H., *Dtsch. Z. Nervenheilk.*, 1958, **178**, 330.
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PORTAL HYPERTENSION

Portal hypertension in association with hepatic cirrhosis is a pathological syndrome which may endanger life, both by haemorrhage from gastro-oesophageal varices and by progression of the liver disease to hepatic failure. In patients with this syndrome the creation of a portosystemic venous shunt constitutes the most effective treatment available to arrest or prevent haemorrhage, but it is available to determine pre-operatively not only that the patient will survive the acute deviation of portal blood from the liver, but also, if possible, the ultimate prognosis of the associated hepatic disease.

Surgeons undertaking these operations recognize that the clinical appreciation of the patient is of paramount importance in making this assessment, but additional information from radiological, histological, and biochemical investigations may both influence the immediate treatment and indicate the nature of the cirrhosis and its possible mode of progression. In a recent article[1] A. H. Hunt and H. Lehmann recorded their personal experiences with a number of biochemical tests in patients with hepatic cirrhosis and portal hypertension undergoing portosystemic venous shunt operations. They concluded that the levels of serum albumin and serum pseudocholinesterase are two of the most valuable biochemical investigations in these cases. Their statement that a portosystemic venous shunt should not be performed unless the serum albumin is 3.2 g. per 100 ml. is in general agreement with the views of other authorities in this field, though a value below this figure may occasionally be accepted when haemorrhage from gastro-oesophageal varices cannot be controlled by other methods of treatment.

Hunt and Lehmann's observations relating the level of pseudocholinesterase to the severity of the cirrhosis and the long-term hepatic function are perhaps of more interest. In a careful study over a number of years they have found that this test is of value as a prognostic index of whether or not liver function will deteriorate. They suggest not only that levels below 55 units are almost certainly diagnostic of liver disease, but also that the lower the value of this enzyme the more likely is the patient to die of hepatic failure. The authors of this article have been at pains throughout to stress that the clinical appraisal of the patient is of the utmost importance, but if their work on serum pseudocholinesterase can be extended and confirmed by other workers in this field, it may be that an additional test of liver function has been elaborated which will be of value to patients and clinicians alike.

[1] Hunt, A. H., and Lehmann, H., *Gut*, 1960, **1**, 303.

Clinicopathological Conference

A CASE OF HAEMOLYTIC ANAEMIA

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with a haemolytic anaemia who died, aged 78, in Hammersmith Hospital after a terminal diarrhoeal illness (Case No. 77,935; P.M. No. 8,632).

Clinical History

Dr. J. G. SCADDING: The case we have to discuss to-day is that of a man born in 1880, who worked on the maintenance of London Transport Board buses until his retirement about 1950. He suffered from nerve deafness gradually developing since 1929, which made it rather difficult during his final illness to obtain a clear account of his symptoms.

In 1939 he was investigated at Hammersmith Hospital for attacks of vertigo, attributed to Ménière's syndrome. In 1950 the prostate was removed at the West London Hospital because of acute retention of urine: the prostate was reported to be non-malignant. In 1953 he was admitted on the surgical side at Hammersmith Hospital complaining of nausea and occasional vomiting. A barium meal was said to show stretching of the duodenal bulb and circuit by a mass probably connected with the head of the pancreas. Three months later the symptoms subsided and a repeat barium meal showed no abnormality. An intravenous pyelogram at this time showed no evidence of excretion from the left kidney.

DYSPNOEIC AND WEAK

In June, 1957, he attended the out-patient department complaining of increasing dyspnoea and weakness and constipation for six months, and was admitted for investigation. On admission he was well nourished, very pale, and slightly jaundiced. The pulse was of collapsing quality and normal rate. The blood pressure was 215/90. The spleen was palpable two fingers' breadth below the costal margin. There was an aortic systolic but no diastolic murmur. Several small haemorrhages were seen in the ocular fundi. Examination of the blood showed haemoglobin 5.4 g./100 ml.; packed-cell volume 17%; mean corpuscular haemoglobin concentration 32%; reticulocytes 51%; polychromasia and anisocytosis; leucocytes 8,000/c.mm., with a normal differential count; two nucleated erythrocytes to every 100 leucocytes; platelets 220,000/c.mm. The blood contained 2.4 mg./100 ml. of bilirubin. The direct Coombs test was strongly positive. The urine contained a great excess of urobilinogen. Red-cell survival studies showed 20 times the normal rate of destruction with a mean cell life of 5–6 days. Occult blood tests of stools were negative. Phosphatase levels in blood were normal. The blood Wassermann reaction was negative. The sternal marrow was cellular with erythroid hyperplasia (myeloid: erythroid ratio—0.2:1, cf. normal 2.5–15:1).

A clinical diagnosis of idiopathic haemolytic anaemia was made, and he was treated with prednisone, 20 mg. daily. The haemoglobin rose to 9.4 g. and the reticulocytes fell to 18.2% by the time of his discharge from hospital at the end of July, 1957. He continued to attend the out-patient department, prednisone dosage

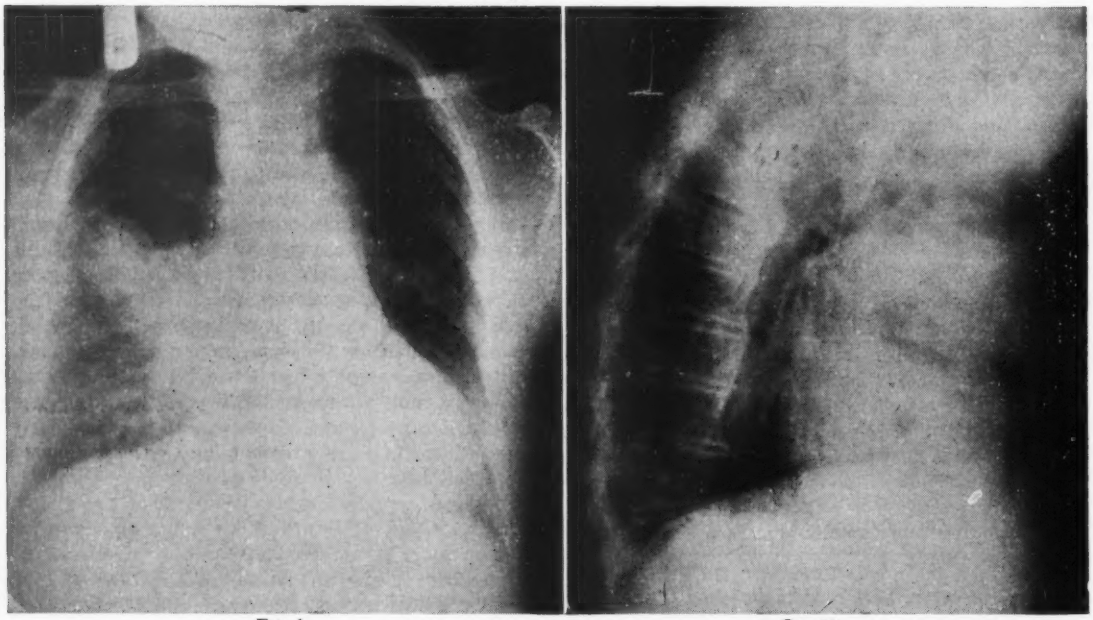


FIG. 1*a* FIG. 1*b*

FIG. 1.—(*a*) Postero-anterior radiograph of chest showing shadow in the anterior segment of the right upper lobe and at the right hilum. (*b*) Lateral radiograph of chest showing the shadow in the anterior segment of the right upper lobe.

was maintained at between 15 and 30 mg. daily, and the haemoglobin level remained between 8.8 and 11.8 g./100 ml. Management was complicated by disturbances of mood, with depression and agitation, for which he was given meprobamate. Towards the end of 1957 he complained for the first time of angina of effort.

ACUTE ILLNESS

On September 21, 1958, he was readmitted because of abdominal pain, vomiting, and pain in the right shoulder of four days' duration. On admission he looked ill, but his nutrition was well maintained. The pulse was irregular, 100 per minute. There was irregular low fever, up to 100° F. (37.8° C.). There was slight jaundice (bilirubin 2.3 mg./100 ml.). The spleen was palpable one finger's breadth below the costal margin. There was no abdominal tenderness or other abnormality on palpation. Rectal examination showed nothing abnormal except a few nodules in the left lobe of the prostate, which was small, and an enlarged right lobe. In view of the history of prostatectomy, it was not possible to say whether these nodules were due to carcinoma or not. In view of this, acid phosphatase levels in the blood were estimated, and were normal. A chest radiograph showed a shadow in the anterior segment of the right upper lobe and at the right hilum (Figs. 1*a* and 1*b*). Treatment with prednisone, 22.5 mg. daily, was continued, and in the first instance with tetracycline and novobiocin on the supposition that the shadow in the chest radiograph might represent an inflammatory consolidation. Sputum culture produced only coliform bacilli and *Streptococcus viridans*. The haemolytic anaemia continued to be partially controlled by prednisone: serial examinations during the rest of his life showed the haemoglobin to be maintained at about the same level, reticulocytes remaining around 10%, and the mean red-cell life was estimated at 15 days. I will say no more about this aspect of his case, since clinically it seemed to have no direct relationship with the events of the terminal part of the illness, but Professor Dacie will no doubt deal with it more fully later in the discussion. Electrocardiography showed the irregularity of the pulse to be due to atrial tachycardia with a wandering pacemaker, the P wave varying in shape and direction. There was also considerable left ventricular enlargement.

"TROUBLESOME DIARRHOEA"

His progress was unsatisfactory. Shortly after admission troublesome diarrhoea developed; I will discuss this later, but first describe the puzzling evolution of the lung changes. The shadow in the right lung persisted, and a small pleural effusion developed (Fig. 2). This was sterile and contained no malignant cells. The patient was considered too ill for bronchoscopy under general anaesthesia and too uncooperative under local analgesia. On the admittedly remote chance that the intrathoracic changes might be due to a reticulosis, which might link with the haemolytic anaemia, deep *x*-ray treatment was started at the end of October, but was stopped after 12 days, largely because the abdominal symptoms were becoming more prominent. The intrathoracic changes showed little change, but a radiograph on December 1 showed considerable diminution both in the shadow in the anterior segment of the upper lobe and in the pleural effusion. Investigation of the diarrhoea was inconclusive. Repeated stool cultures gave no useful information, showing no potential pathogens until a few days before death, when *Pseudomonas pyocyanea* was reported. Neomycin, to which this organism was sensitive, was given without effect on the diarrhoea. Sigmoidoscopy was difficult because of poor co-operation and persistent flooding by liquid faeces, and was inconclusive. In spite of supportive treatment, he gradually deteriorated and died on December 11, 1958.

Clinical Diagnosis

(1) Idiopathic haemolytic anaemia treated for 18 months by prednisone.

(2) Lung changes, possibly inflammatory, but malignant disease not excluded.

(3) Chronic diarrhoea of undetermined cause, the diarrhoea being the precipitating cause of death.

Post-mortem Findings

Dr. J. G. AZZOPARDI: The body was that of a well-nourished man. There was a suprapubic scar, pitting oedema of the ankles, and a small bedsore over the right side of sacrum.

The *heart* weighed 540 g. (normal 380 g.). The left ventricular wall was hypertrophied, averaging 18 mm. at the base. Right ventricle: 4 mm. Valvular orifices were normal. The aortic valve cusps were slightly thickened at their insertions. There was an irregular area of whitish fibrous tissue, 1 cm. in diameter, at the base of the posterior papillary muscle of the left ventricle. The right coronary was dominant. The coronaries showed marked atheromatous flecking with narrowing, but no gross occlusion of the main vessels. Microscopic examination showed hypertrophied fibres and the fibrous residue of an old posterior infarct (Fig. 3). There was mild discrete atheroma in the thoracic and moderate discrete atheroma in the abdominal aorta. Great veins normal.

The *upper respiratory passages* and *larynx* were normal. Mucosa of *tracheo-bronchial tree* reddened,

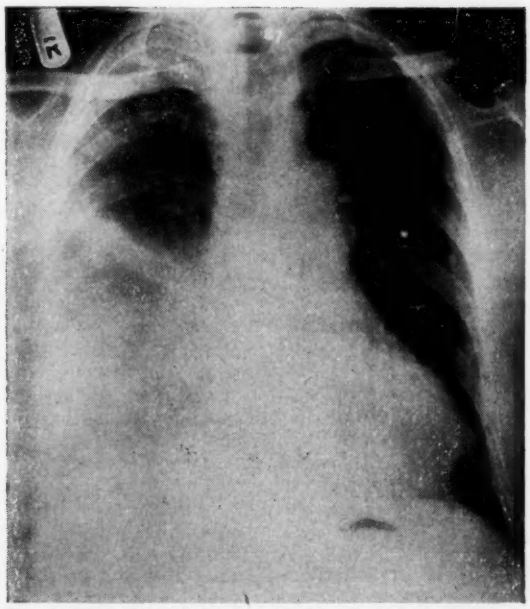


FIG. 2.—Postero-anterior radiograph of chest showing persistence of shadow in the right lung, with a small pleural effusion.

with a little thick mucus in the lumen. Right lung weighed 850 g. and the left lung 820 g. Both were moderately oedematous. In the posterior basal segment of the right lower lobe there was a wedge-shaped fibrous subpleural area, $3 \times 1 \times 1$ cm. An apical scar was the only significant finding in the left lung. Microscopically, the scar in the right lung was shown to be a healed infarct showing preservation of the alveolar elastic framework with gross collapse (Fig. 4). The artery to this segment contained an organized thrombus ringed with haemosiderin granules (Fig. 5). The remainder of the lung parenchyma showed very small foci of bronchopneumonia in which macrophages predominated over polymorphs. The right pleural space was obliterated by dense adhesions, the visceral pleura being converted over large areas into a thick fibrous sheath. The horizontal fissure was obliterated by a similarly altered pleura. The left pleural space was obliterated by loose adhesions and there was 100 ml. of straw-coloured fluid.

The *right kidney* weighed 140 g. and the *left kidney* 180 g. (normal 170 g. each). Their capsules stripped easily, leaving finely pitted, slightly moth-eaten surfaces. On the cut surfaces the cortex appeared pale and slightly irregular in width. The corticomedullary junction was fairly sharp. *Urinary passages* and *bladder* normal. Microscopic examination showed fibroelastosis of arcuate arteries and intralobulars consistent with the age and hypertensive state. There was a marked vacuolation of the first convoluted tubules (Fig. 6) resembling that seen in sucrose nephrosis, and possibly the result of hypokalaemia. *Prostate* of average size despite previous surgery, normal histologically. *Testes* normal.

The *spleen* weighed 260 g. (normal 170 g.). Its surface was covered by peritoneal adhesions. The cut surface showed a soft, uniform, reddish-brown pulp with inconspicuous follicles. Strongly positive Prussian-blue test for iron. Microscopy showed abundant haemosiderin in the red pulp of the spleen. *Vertebral, sternal, rib,* and *iliac crest* marrow pink and cellular. Histologically, marrow slightly hyperplastic. In the femur, active marrow extended down into the upper quarter of the shaft. Vertebral bone was rather soft, with a moderate degree of osteoporosis. No *lymph node* enlargement.

Mouth, oesophagus, stomach, and *duodenum* were normal. A diverticulum was present two feet (0.6 m.) distal to the duodenojejunal flexure. The small intestine was otherwise normal, grossly and histologically. The *large intestine* was grossly altered from caecum to rectum. The mucosa was reddened, thickened, and oedematous and studded throughout with numerous closely set polypoid projections (Fig. 7), averaging 8 mm. in diameter and projecting 3 mm. above the surrounding surface. The projections were mushroom-shaped and had a greenish-yellow tinge as if necrotic on the surface. Microscopically (Figs. 8 and 9) the inflammatory nature of the "polyps" was shown. These were covered superficially with a necrotic slough mixed with fibrin. Beneath this the occluded colonic crypts were distended into saccules containing mucus and a few polymorphs. The lamina propria was oedematous and infiltrated almost exclusively by plasma cells. A few Gram-negative bacilli were found in the superficial part of the lesions. This peculiar colonic lesion was probably the result of an infection with *Ps. pyocyanea.* The *liver* weighed 1,470 g. (normally 1,600 g.), and had a normal architecture. There was moderate fatty change (Fig. 10) affecting particularly the periportal areas. The Kupffer cells contained a small amount of iron-containing pigment. The *gall-bladder* contained thick bile and the biliary passages were normal. The *pancreas* was enlarged and weighed 140 g. It was very greasy and on section was found to consist almost entirely of adipose tissue, with only scattered small greyish-white streaks of pancreatic parenchyma. In spite of its size, the total parenchyma appeared markedly reduced, a condition of lipomatous pseudohypertrophy. The main pancreatic duct appeared normal.

Pituitary normal. *Thyroid* gland (28 g.) slightly enlarged for the age: it contained one or two small, microfollicular nodules. *Adrenals* (14 g. together) showed depleted lipid. *Meninges* normal. The *brain* weighed 1,450 g. (normal 1,400 g.), and appeared normal apart from a slight dilatation of the ventricular system.

Pathologist's Diagnosis

(1) Idiopathic haemolytic anaemia.

(2) Dense right pleural adhesions. Small resolving foci of bronchopneumonia.

(3) *Ps. pyocyanea* colitis with hypokalaemic changes in proximal convoluted tubules of kidneys.

(4) Healed posterior myocardial infarct.

(5) Lipomatous pseudo-hypertrophy of the pancreas.

Discussion

Professor J. V. DACIE: The diagnosis of acquired haemolytic anaemia was based on finding evidence of excessive haemolysis, with anisocytosis, polychromasia, and increased osmotic fragility, and in particular a strongly positive direct Coombs or antiglobulin test. We managed to show that his red cells had absorbed gamma-globulin by demonstrating that the antiglobulin reaction could be inhibited by adding very small amounts of gamma-globulin to the rabbit antiglobulin serum. The antibody was the warm type, and it acted on all types of blood cells tested, including, of course, his own. We couldn't therefore demonstrate any specificity. The first slide (a blood film) illustrates anisocytosis and spherocytes; the small cells, which have been acted upon by antibody, stain rather deeply. The next slide is a photograph of bone marrow. This shows excessive erythropoiesis, of which the high reticulocyte count in the peripheral blood was a reflection. Normoblasts in all stages of development are present.

SITES OF BLOOD DESTRUCTION

The next slide illustrates a radioactive-chromium survival study; his own red cells were labelled with a tracer dose of chromium and put back into the circulation. You can see that the cells disappeared fairly rapidly. When the experimental points were plotted on semilogarithmic paper a straight line could be fitted to them. The mean cell life-span is given by the time when 37% of the cells were surviving, approximately 10 days in this case. After steroid therapy the cell survival was considerably lengthened. With the radioactive-chromium technique you can combine surface counting over the liver and spleen with a cell-survival study, and get an idea of where the cell destruction is taking place. In this patient we could show an excess accumulation of radioactivity over the liver as well as over the spleen. The occurrence of haemolysis within the liver and probably elsewhere in the body as well as in the spleen is the reason why so many cases of

FIG. 3.—Edge of healed myocardial infarct showing dense fibrous tissue in centre of photograph. (×106.)

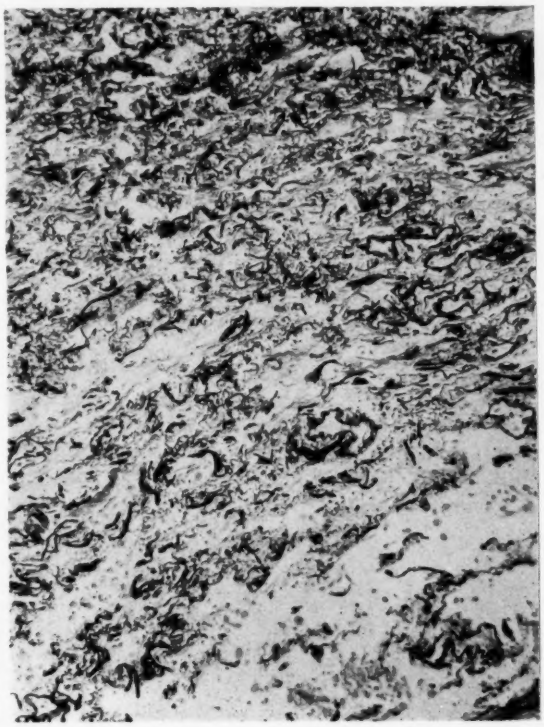


FIG. 4.—Edge of pulmonary infarct showing collapsed alveolar elastic framework (contrasting with normal lung at lower right corner). (×106.)

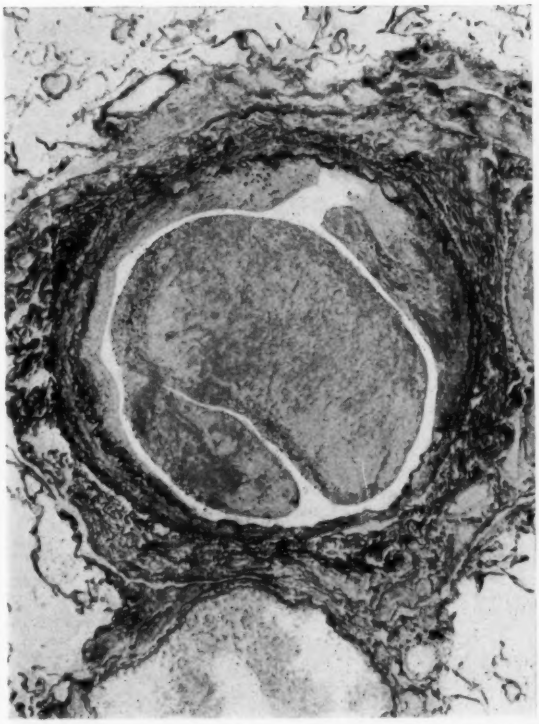


FIG. 5.—Organized thrombus in pulmonary artery containing haemosiderin deposits (appearing as black granules at edge of thrombus). (×47.)

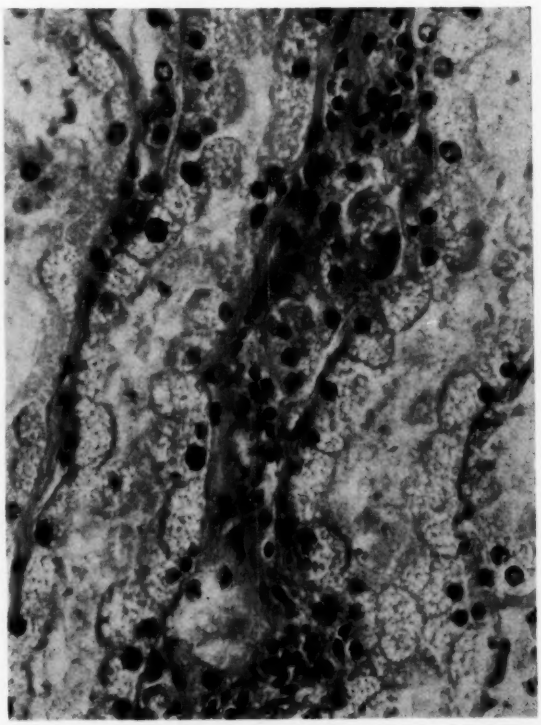


FIG. 6.—Fine vacuolation of proximal convoluted tubules of kidney. (×386.)

FIG. 7

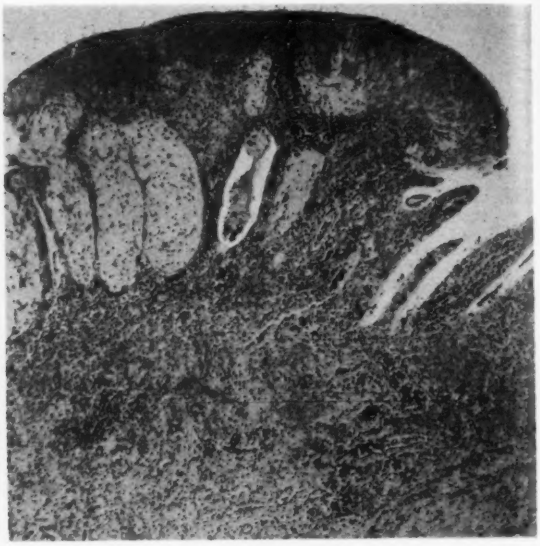


FIG. 8

FIG. 7.—Colonic mucosa studded with closely set inflammatory nodules, many of which are necrotic on the surface.

FIG. 8.—Edge of one of the nodules in Fig. 7. There is distension of crypts with pale-staining mucus caused by necrosis of the superficial mucosa. (×53.)

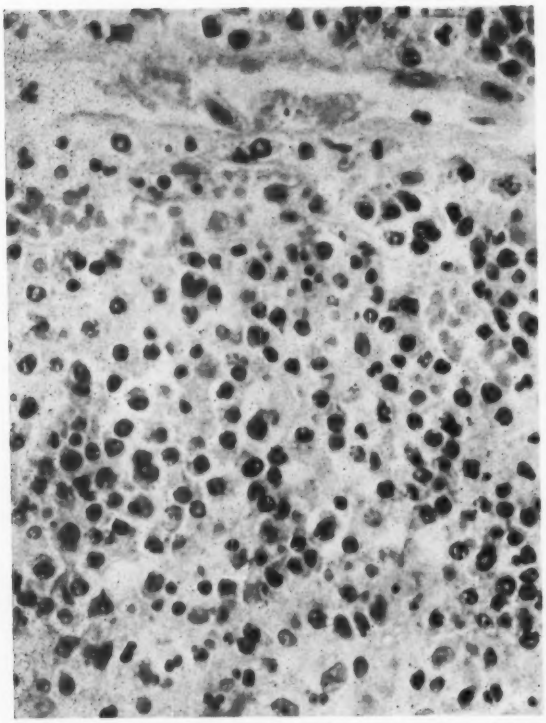


FIG. 9.—High magnification of the inflammatory infiltrate in the nodule shown in Fig. 8. Plasma cells predominate. (×470.)

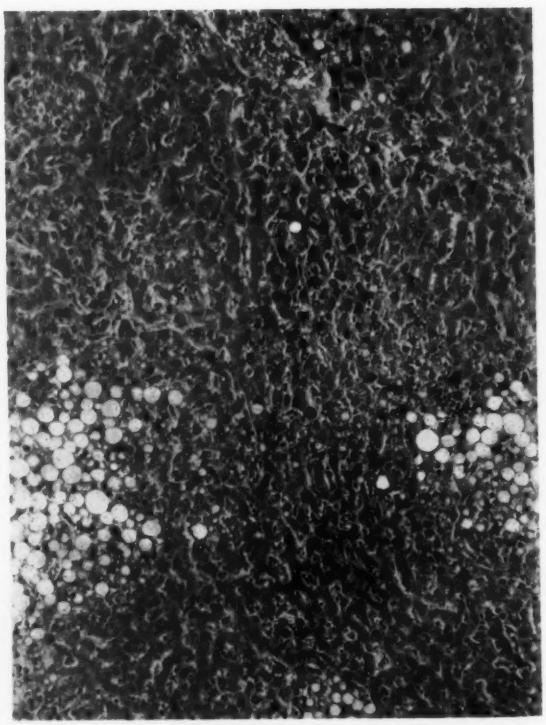


FIG. 10.—Liver with fatty change predominantly periportal in distribution. (×106.)

acquired haemolytic anaemia do not do particularly well after splenectomy; you can remove one site of blood destruction, but you cannot influence the blood destruction going on in the liver. The present patient was an old man and splenectomy was never contemplated, and he did in fact respond quite well to steroids. But if we had undertaken splenectomy, I don't think we could have done it with any expectation of a major degree of relief.

HEART AND LUNGS

Professor J. MCMICHAEL: Dr. Scadding, would you like to add anything to your previous remarks?

Dr. SCADDING: I'm really left with a series of questions I would like to ask rather than anything more I can contribute. I should like to clear up one point; there was in fact some electrocardiographic evidence of the infarct. I didn't mention it because of the length of the clinical history, but there was a depression of the ST intervals in leads 1, 2, V2, V3, and right over to V7, which were reported as compatible with ischaemia but with a query whether some of this might be due to tachycardia. In a man of 78 one perhaps wouldn't be surprised at such changes.

So far as the pulmonary condition is concerned, our first thought was that the shadow we saw there at the beginning might be due to inflammatory causes, but there are two things that made us doubt that opinion later. One was the site of the shadow, in the anterior segment of the right upper lobe, which is a somewhat unusual position for an isolated inflammatory change; and the second was that there was no response of the sort one would have expected to treatment with antibiotics. Of course it would have been the correct thing, in a patient in better general condition, to have done a bronchoscopy at that stage, but we didn't do that in this patient for two reasons. First, he was a very ill old man, and was almost completely deaf, so that a bronchoscopy under local analgesia would have been extremely difficult, not least for the patient himself, and a general anaesthetic for a bronchoscopy would have been dangerous. And secondly, even if there had been a growth in that anterior segment, my expectation of useful information from a bronchoscopy would be very small, because a growth in the anterior segment of the upper lobe may very well give rise to no abnormality in any visible part of the bronchial tree. Even if we had bronchoscoped him and had seen nothing, we would not have been able to say he had not got a bronchial carcinoma, so a bronchoscopy would have made no practical difference to our management of this difficult case. For these reasons we did not bronchoscope him, but decided instead to try the effect of radiotherapy. We were encouraged in this by the remote possibility that, in view of the apparent enlargement of the mediastinal shadow, we might be dealing with a reticulosis which might be more sensitive to radiotherapy than a bronchial carcinoma. However, events showed that we were wrong in both those suppositions even before the pathologists demonstrated it so well as they did.

There are two outstanding points on which I would like elucidation. One is the question of *Pseudomonas* colitis, about which I would like to learn a little at this conference; and the other is whether the change found in the pancreas had any relation to the curious condition which was investigated on the surgical side in 1953 when there was said to be some abnormality, in the barium meal examination, in the shape and disposition of the duodenal circuit.

"IDIOPATHIC" HAEMOLYTIC ANAEMIA

Professor MCMICHAEL: Professor Dacie, is this in fact a primary haemolytic anaemia of unknown causation appearing in a man of this age, or has it some connexion with his other illnesses?

Professor DACIE: I would have thought that this was in fact a primary or so-called "idiopathic" haemolytic anaemia. There must, of course, be some cause, but I think we have to admit that the cause and mechanism in such cases are still unknown. It is fashionable nowadays to attribute auto-immune haemolytic anaemia to some abnormality in the antibody-forming cells in that they lose their normally foetally acquired immune tolerance to normal red-cell antigens and start developing antibodies against these antigens. Even if this is a correct description of the process, it is not known why this happens. It has been suggested that somatic mutation takes place, or, alternatively, that a virus, perhaps acting on the antibody-forming tissue, alters in some way its capacity to react to stimuli which are not normally antigenic. It really is a complete mystery.

INFLAMMATORY RESPONSE AFTER STEROIDS

I'd like, if I may, to ask a question: I have an uncomfortable feeling that the inflammatory changes are in some way secondary to the long steroid therapy he had had. He was treated with prednisone at a dose of up to 30 mg. a day for about 15 months. I would like to have some other views on whether this in any way lowered his resistance to infection.

Professor MCMICHAEL: Well, that was just passing through my mind, too. His inflammatory reactions were of a very abnormal character—macrophage reactions in the lungs, and, I think, plasma cells dominated in the wall of the colon—and yet there is no reason haematologically why he should have had such poor polymorph response, is there?

Professor DACIE: No. I don't think so. His leucocyte count was adequate: total, 8,000 per c.mm. with 78% neutrophils. I don't believe he was neutropenic at any time.

Dr. J. G. AZZOPARDI: I think that Dr. Williams has studied the reactions to *Ps. pyocyanea*—I see him at the back there, so maybe he will be able to tell us about this peculiar response and the relative lack of polymorphs in these cases.

PYOCYANEA COLITIS

Dr. MARY BARBER: I think there are several things on the pyocyanea side. Nobody has seen very many such cases, but one or two people are saying that they have seen very severe forms of rather unusual colitis which appear to be due to *Ps. pyocyanea.* It is only fair to the Bacteriology Department to point out that we did report this during life and went out of our way to show that it was a significant report by saying that the faeces contained a heavy growth of *Ps. pyocyanea* and a complete absence of *Bact. coli.* You say here that the stool cultures gave no useful information; I think it is only fair to Dr. Scadding to add that this report came out late—in December and the patient died on December 11—but at any rate it was a

very significant finding. Actually *Ps. pyocyanea* was present in the patient's faeces as early as November 8.

I think undoubtedly the combination of prednisone and the antibiotics—and may I point out that the antibiotics given included tetracycline, which is very important, because tetracycline gets rid of all the normal flora of the gut?—played an important part. I just wonder whether it would be worth considering in such cases, if you are going to give both broad-spectrum antibiotics and prednisone, giving a drug-resistant lactobacillus by mouth. There is such a preparation on the market. It is called "enpac." I think Dr. Williams has studied the histology of infection with *Ps. pyocyanea* and might give some information on that.

Sir WILLIAM MORROW (Sydney): I wouldn't like to say I've seen a case exactly like this. I just wonder whether the colonic lesion was in fact a sensitivity to the broad-spectrum antibiotics, with superimposed infection.

Dr. E. D. WILLIAMS: I would entirely agree with Dr. Mary Barber that steroids, certainly in the leukaemias, tend to increase the incidence of *Ps. pyocyanea* septicaemia,* and in this case the pyocyanea infection certainly played a part in the fatal termination. It is difficult to be certain about the suggestion of antibiotic sensitivity. I see, however, he had the antibiotics for a considerable time, and, as the severe diarrhoea came on coincidentally with the findings of *Ps. pyocyanea* in the stools, I feel the organism is the more likely cause. As regards the histology, pyocyanea infection has been said to induce no great polymorph response; this is a little difficult to interpret, because so many of the infections with *Ps. pyocyanea* have been in leukaemic patients who may have anyhow been unable to turn out normal polymorphs in any numbers. We have had one other case of pyocyanea colitis in a non-leukaemic patient with a similar histological picture, so I think one would be forced to conclude that the likely diagnosis was a pyocyanea colitis. The histology, showing recent ulceration with oedema and a predominantly non-polymorphonuclear inflammatory response, would fit in well.

Dr. BARBER: There was one case—I don't know whether anyone remembers this—a patient who died quite recently with a pyocyanea colitis. It was a very severe colitis in a patient who had had a gastrectomy and broad-spectrum antibiotics, but not prednisone.

Dr. WILLIAMS: I remember that one particularly well because he had a tap-water enema and we suspected this as a possible source of infection.

SPUTUM CULTURE

Dr. AZZOPARDI: Dr. Barber, did you find anything in this man's sputum, did you find *Pseudomonas* in particular?

Dr. BARBER: He did have *Pseudomonas* in his sputum.

Dr. AZZOPARDI: Where would the infection have come from, do you think?

Dr. BARBER: Well, possibly from the gut. It seems to me that many people in health will yield one or two colonies of *Ps. pyocyanea* in the faeces perhaps, but the normal flora—i.e., *Bact. coli* and *Strep. faecalis*—keeps them under. The infection in this patient may therefore have been an auto-infection.

*See "Fatal Case of Granulocytopenia," *Brit. med. J.*, 1961, 1, 1525.

Dr. SCADDING: I feel there is a factual contribution I can make to this discussion; that is, the detail of the antibiotics he received, which I did not give in the brief summary. He did in fact have a great deal. For six days after his admission he received 2 g. of tetracycline and 1 g. of novobiocin a day—i.e., from September 23 to 28: thereafter he had none until the end of October, when for a fortnight he received rather similar treatment, not quite the same dose; then he had no further antibiotics until we gave him neomycin 2 g. daily, starting on December 4. I emphasize that he was receiving neomycin from this date, in order to defend the statement in my summary that stool cultures gave no useful information. We received the information that *Ps. pyocyanea* was there only a few days before death and at a time when he was already receiving neomycin, to which the *Pseudomonas* was alleged to be sensitive.

Professor J. W. CROFTON (Edinburgh): May I ask when the diarrhoea started? Was the first culture soon after the diarrhoea began?

Dr. SCADDING: Oh, a long, long time after. The diarrhoea had been going on since September and we got the report at the beginning of December.

Dr. BARBER: *Ps. pyocyanea* was found in the faeces on November 8.

Professor CROFTON: Can you probably suggest then that the whole of the diarrhoea was due to *Ps. pyocyanea*?

PANCREATIC PSEUDO-HYPERTROPHY

Professor MCMICHAEL: Dr. Booth, can you help us about this pseudo-hypertrophy of the pancreas?

Dr. C. C. BOOTH: Well, I am a little worried about this case. I don't know much about pseudo-hypertrophy of the pancreas, but it is quite possible, as Dr. Scadding says, that it could widen the duodenal loop, though it is a little odd that this wide ring should have disappeared when he was *x*-rayed three months later. But what really worries me is the view that a normal inhabitant of the colon can suddenly turn against that colon and begin to destroy it.

Dr. BARBER: I am not quite prepared to admit that *Ps. pyocyanea* is a normal inhabitant of the colon: in saying it was present in a few normal people, I didn't mean to infer it was normal.

AUTO-IMMUNE DISEASE

Dr. BOOTH: I'm sure that, if we were in Melbourne to-day, we should be told that this was a case of auto-immune disease, starting as the development of an antibody to red cells and then also affecting the colon. I think this is an alternative thought whether you believe in these things or not. I'm not completely sold on the question of *Ps. pyocyanea* here.

Professor MCMICHAEL: I would like to just come back to Professor Dacie and ask him if auto-immune disease spreads from system to system.

Professor DACIE: This is a debatable point. I wouldn't like to make any pronouncement on this. I would have thought personally it was unlikely in this case that the colon was involved in the auto-immune process, but I must admit I have very little evidence for or against.

Professor MCMICHAEL: Dr. Steiner, you wanted to say something.

RED HERRINGS

Dr. R. E. STEINER: I've got little doubt that the wide duodenal loop was due to the enlarged head of the pancreas—why there should have been a fluctuation in size, I don't know. A question I would like to ask: is there any evidence at all that this man has had pancreatitis? Another point, a further red herring, he had ankylosing spondylitis and this has never been mentioned but there is definite evidence of it radiologically.

Dr. BOOTH: Well, ankylosing spondylitis may be associated with ulcerative colitis, a condition thought by some to have an auto-immune basis. It makes one wonder whether this was some primary type of auto-immune disease involving the colon which had ultimately been influenced by the *Ps. pyocyanea*. This is no less likely than that *Ps. pyocyanea* was the primary factor involving his colon.

Dr. BARBER: I think that is quite possible in this case.

Professor MCMICHAEL: Well, I think I've shown remarkable restraint in keeping off the very interesting fact that he had a scarred kidney and hypertension!

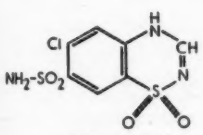
We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

To-day's Drugs

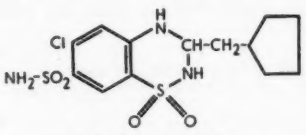
Cyclopenthiazide

"Navidrex" (Ciba).

Chemistry. — This is 6-chloro-3-cyclopentylmethyl-3,4-dihydro-7-sulphamoyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide, and, as the formulae show, is a derivative of chlorothiazide:



Chlorothiazide



Cyclopenthiazide

Pharmacology.—Cyclopenthiazide is an oral diuretic, and the pattern of electrolytes excreted in the urine suggests that its action is similar or identical to that of chlorothiazide and hydrochlorothiazide. The loss of sodium and chloride is approximately equimolar. Increase in excretion of bicarbonate is so slight that the compound must cause little inhibition of carbonic anhydrase. Excretion of potassium is increased, and the evidence is insufficient yet to show whether it is greater or less than after other benzothiadiazine diuretics; physiological principles suggest that there is unlikely to be any significant advantage or disadvantage in this respect. Cyclopenthiazide induces within 1–2 hours a diuretic action which reaches its maximum in 4–8 hours and is complete in about 12 hours.

Therapy.—The drug may be used for the relief of oedema caused by cardiac, hepatic, or renal disease. It also potentiates the action of antihypertensive agents. The tablets contain 0.5 mg., and maximum effect is achieved with a dose of 2 mg. Initially 2 tablets daily will usually be necessary, but when the oedema has largely subsided treatment should be intermittent: 0.25–0.75 mg. (½–1½ tablets) on two or three mornings each week. There is not enough evidence at present to say whether cyclopenthiazide, which is certainly more potent on a weight basis than any other benzothiadiazine compounds, has any clinical advantage over the longer-established diuretics in this series.

Side-effects.—No toxic effects have yet been reported, but depletion of potassium may develop, causing intolerance to digitalis in cardiac failure and precipitating coma in cirrhosis of the liver. When treatment has to be prolonged and the patient's appetite is poor, supplements of potassium are necessary. In common with similar diuretics, cyclopenthiazide may induce an attack of gout in susceptible subjects.

N.H.S. Basic Price.—100 tablets, 15s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Medical and Surgical Vagotomy

SIR,—We were interested in the paper by Mr. I. E. Gillespie and Professor A. W. Kay (June 3, p. 1557) on "The Effect of Medical and Surgical Vagotomy on the Augmented Histamine Test in Man." A reliable method of evaluating a patient's response to vagotomy would be of inestimable value in surgery and help greatly in the selection of patients for operation. This is the claim of the above paper, but there are some basic difficulties remaining that received insufficient attention.

In the series of 40 patients presented, although in the main there is good correlation between the effects of medical and surgical vagotomy, 10 cases showed a small reduction in gastric acidity as a result of medical vagotomy. Of these, four subsequently showed a poor result from surgical vagotomy (in terms of gastric acidity), and six showed a much larger reduction in acidity following surgery. This type of variation renders accurate assessment of the individual patient difficult. In a series of 91 surgical vagotomies[1] we found that clinical results could not be correlated with tests of gastric acidity. In some cases, patients who developed a high level of gastric acidity following vagotomy remained free of symptoms, and in other cases a low level of acidity was associated with recurrent ulceration.

The results of gastric-acid evaluation can only be of value where the specimen is collected from an intact stomach with a functioning pylorus. Where gastrectomy has been performed, or gastro-jejunostomy or a pyloroplasty (i.e., a drainage operation), the testing of gastric acidity obviously loses much of its value by reason of the rapid drainage of gastric acid into the upper intestine and the reverse flow of alkaline upper-intestinal juice into the stomach or stomach remnant. We feel that these variations may preclude medical vagotomy from giving an exact estimate of the expected result from surgical vagotomy. It is also impossible to ensure that medical vagotomy by injections of atropine sulphate and hexamethonium bromide is complete in all cases in the doses used. The authors admit that the test may be defective in certain cases. For these reasons we feel it is unsound to base any exact scheme of treatment on the results of tests for gastric acidity.—We are, etc.,

P. G. BEVAN.
B. N. BROOKE
G. SLANEY.

Department of Surgery,
Queen Elizabeth Hospital,
Edgbaston, Birmingham 15.

REFERENCE

1 Slaney, G., Bevan, P. G., and Brooke, B. N., *Lancet*, 1956, 2, 221.

SIR,—Mr. I. E. Gillespie and Professor A. W. Kay (June 3, p. 1557) in their interesting article present good, hard-won evidence that the extent of reduction of gastric acidity after complete vagotomy is widely variable, with most patients showing a fall greater than 50%, but that in one-tenth it is less than 35%. They contend, therefore, that in some patients removal of the hormonal mechanism of acid production by antrectomy may be necessary in addition to vagotomy to prevent recurrent ulceration. The converse has been familiar for some time, that removal of the hormonal mechanism (included in a two-thirds gastric resection) reduces the level of acid sufficiently to allow most duodenal ulcers to heal, but that a few patients need removal of all acid-secreting cells by a very high partial gastrectomy or by adding vagotomy. They conclude that "this combination of operations [vagotomy and antrectomy] probably offers the best protection against recurrent ulceration" (with which I agree, for I have been performing antrectomy and vagotomy since 1951 and cannot find an instance of recurrence in a series just short of 250 such operations), and they continue, "but by reintroducing the hazards of closure of the duodenal stump the immediate mortality is greater than that associated with simple vagotomy."

Why then reintroduce hazards by closing the duodenal stump? Why not leave it wide open and anastomose it to the reconstituted end of the open stomach, thus leaving things much as nature made them? Leakage then of any consequence is rare, and, if it should occur, it settles well if the stomach is kept empty by aspiration. A gastroduodenal anastomosis will also eliminate their other worries about rapid gastric emptying through a gastrojejunal anastomosis. Further, well-known caprices of loops of small gut associated with gastrojejunal anastomosis cannot occur.

When gastric resection is limited to antrectomy the gastric and duodenal ends fall easily together without tension, and such is the remaining gastric capacity that no troublesome syndrome from a small stomach occurs. In a personal series of well over 300 gastroduodenal anastomoses after resection for duodenal ulceration no patient was lost due to leakage at the anastomosis. Only one was lost because of the dissection of the ulcer. Most resections of a portion of duodenum for ulceration are easy and safe. In the few instances where the ulcer is very deep and the scarring is dense there is good reason for abandoning any attempt at the preferable procedures of pyloroplasty or antrectomy and for settling for vagotomy and gastroenterostomy regardless of pre-operative secretory performance. There is always the chance for another try in a live patient.—I am, etc.,

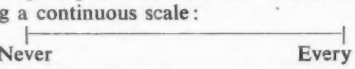
The Radcliffe Infirmary, Oxford. G. E. MOLONEY.

Subjective Assessment in Clinical Research

SIR,—The application of scientific methods to clinical research has grown over the years, and techniques have been developed for subjective assessment which are amenable to statistical analysis. Many workers, especially in respiratory disease, have assessed these methods with great care, and recent articles in the *Journal* by Drs. C. M. Fletcher and C. M. Tinker (May 27, p. 1491) and Dr. J. M. Rogan *et al.* (May 13, p. 1337) draw attention to this.

Many techniques, however, use methods which require dichotomous answers to questions that are not truly answerable in such a way. For example, Drs. Fletcher and Tinker ask in the first question of their self-administered questionary: "Do you cough at all during the winter when you first get up?" They ask for the answer to be either "Yes" or "No," and "No" if in doubt. It would seem that the use of such a technique for subjective assessment fails to extract the maximum information, by not providing any quantitative measure of degree, and may even have produced false information by having forced a biased answer from those in doubt. Clarification by further questions or elucidation by an interview may provide more information, but still does not achieve the maximum.

To overcome such difficulties we suggest that a question of this kind be asked in the following way: "How often do you cough during the winter when you first get up?" and that the answer be given by marking a continuous scale:



The patient is instructed to regard the scale somewhat as follows: "If you never cough, put a mark at the extreme left. If you always cough, put a mark at the extreme right. If you cough on average one day in two, put a mark in the centre. If you cough more or less than this, put a mark where you think it will give a fair picture." The answer is scored by measuring the distance of the mark from either end: a 10 cm. line measured to the nearest mm. has proved convenient.

Such a technique provides quantitative measures which are amenable to standard statistical analysis for continuous variables such as analysis of variance. A frequency distribution of the results will provide information in a form suitable for clinical assessment and avoid the important defects inherent in the use of false dichotomies.—We are, etc.,

J. L. GEDYE.
R. C. B. AITKEN.
HELEN M. FERRES.
R.A.F. Institute of Aviation, Farnborough, Hants.

Feeding of Infants before Adoption

SIR,—The letter from Mr. David Maxwell (June 10, p. 1687) prompts me to join the debate he mentions. I know there are two opposing views on the subject of adoption, and after many years' experience of looking after a small home for unmarried mothers, plus the experience of many years in general practice, I have no doubt at all as to my own views.

I feel that in practically all cases where the baby is healthy adoption is the better alternative. A child is entitled to two parents and to be in a home where it is wanted and where it can be treated, both at home and at school, as a normal child. The opposing school of thought—namely, that the mother "should be brought to a sense of her responsibilities"—condemns the child in the great majority of instances to being brought up by a relative or landlady, while the mother goes to work. The mother gets very little outside pleasure or leisure, as her evenings must be absorbed by the child. The result is the child is either resented as a barrier to possible marriage, or becomes the main repository of the mother's emotions, with the possibility of great unhappiness to either or both in the future.

I am fully convinced that in most cases there is no need to stimulate the girl's maternal instinct—it is there,

developing with the pregnancy and culminating with the birth of the child. I am convinced also that the majority of the mothers wish to keep their babies, and it is only a realistic attitude towards the babies' future, and (secondarily) their own, that allows them to permit the child to be adopted. I have been greatly struck by the resulting sense of loss for a long time afterwards, often completely unrealized by the girl and presenting as some form of mild illness. Frequently this is even more intensified if the baby dies at birth or shortly after. On the superficial level this might be looked on as convenient; on the deeper emotional level it is frequently devastating and is very slow to resolve.

These being my sentiments, I consider it cruel for any mother who is likely to part with her baby to be asked to feed it and then to stop, with the resulting physical discomfort and emotional upset. The obstetric unit which deals with the girls I look after has always been most co-operative in this respect, and lactation is suppressed from the beginning.

Mr. Maxwell's quotation of an attitude that the mother should never see her baby is, I think, psychologically unsound. The mother, by the very act of becoming pregnant, has assumed adult responsibilities, and should have her share in seeing her baby, and, guided by the voice of experience, deciding on its future.

You will gather, Sir, that I am all for adoption where possible and no breast-feeding for the unmarried mother.—I am, etc.,

Glasgow W.2. KATE HARROWER.

Canvassing in Medical Elections

SIR,—From time to time I receive letters from various persons not personally known to me, inviting me to vote for some particular candidate for election to some body such as the council of the Royal College of Surgeons, etc. These unconvincing, gratuitous communications follow much the same pattern. They commence with the claim that some branch of medicine or surgery, or that some hospital, needs representation, and then follows an account of the candidate's attainments and activities, to which may be added something to the effect that he is a very good chap and possibly that he is not opposed to blood sports, or has excelled at cricket or soccer, or has some other desirable qualifications.

Surely this form of touting is unnecessary, undesirable, undignified, and, if not unethical, it borders very closely upon it and seems justified only by precedent. When postal ballot papers are sent out for the election of any medical body, they are invariably accompanied by a paper which sets out the qualifications of all the candidates. Some of my colleagues with whom I have discussed this question agree that these soliciting letters are to be deprecated, and I therefore forward this letter in the hope that you will publish it so that members of the profession will take the opportunity of stating their views.—I am, etc.,

Melbourne, Australia. FRANKLYN STONHAM.

Shortage of Dietitians

SIR,—To make this the subject of an annotation (June 3, p. 1597) is timely and wise, and it may be that those responsible for instruction on the subject will at last pay some heed to the present irresponsible attitude to dietetics in most of the medical schools and hospitals. It is obvious that action must be taken quickly to remedy this serious failing in therapeutics. To those of us with some knowledge of dietetics the present instructional courses leading to the Diploma in Dietetics are unnecessarily long and cumbersome—for example, the Institutional Management Diploma in its traditional form is both wasteful of the student's time and in many respects unrelated to modern dietetics.

The Catering and Diet Committee of King Edward's Hospital Fund, under the chairmanship of Dr. Avery Jones, has, as one would expect, suggested a commonsense approach to the subject involving considerable replanning. At present, entry requirements are academically unrealistic and variable, and the actual training course, including the preliminary procedures, is too long and expensive. Also the salaries of dietitians in the hospital service compare very unfavourably with those paid to other ancillary personnel. There is no reason why the course should be longer than three years, but there must be some uniformity in the training offered. A period of more than twelve months in a hospital dietetic department is, in my view, necessary before registration, though it must be appreciated that there are still few establishments, other than the teaching hospitals, that possess a dietetic department suitable for instructional purposes.

There is no doubt that the present appalling lack of support by the medical and particularly the senior nursing staff of hospitals does much to discourage those hoping to make dietetics a career.—I am, etc.,

London N.W.1. J. SHARP GRANT.

Bilateral Rupture of Achilles Tendon

SIR,—I have read with interest the medical memoranda by Mr. G. B. Smaill (June 10, p. 1657) and Drs. M. A. Cowan and Suzanne Alexander (p. 1658), as we have recently had a somewhat similar patient under our care.

A 61-year-old painter was referred to us by Dr. W. S. Hamilton with bilateral rupture of his Achilles tendons associated with disseminated lupus erythematosus controlled by prednisolone. Disseminated lupus erythematosus was diagnosed in September, 1957, when he presented with episodes of haemoptysis. Previous polyarthritis had started in 1955. There were signs of renal damage. He responded well to prednisolone 20 mg. daily. In 1959, as he deteriorated, he was put back on to prednisolone 10 mg. daily. This improved his condition, but, as albuminuria and a high E.S.R. persisted, prednisolone was increased to 20 mg. daily by the end of August, 1959.

In October, 1959, he complained of some discomfort and tightness in the right Achilles tendon, though no abnormality was found apart from a little thickening of the tendon. In April, 1960, he was seen at the orthopaedic out-patient clinic, when bilateral rupture of the Achilles tendons was noted. Surgery was delayed because of his poor general condition and his ability to walk quite well though he complained of a feeling of falling forward. In May, 1961, the question of surgical repair was reconsidered but was not recommended, as, although he had a typical flat gait, he said he had no significant restriction of his activity. He remains on prednisolone 10 mg. daily.

This patient differs from that described by Drs. Cowan and Alexander as no cramps in the calves occurred, though there was an episode of presumed partial rupture in October, 1959, prior to the definite rupture in April, 1960. It is believed that prednisolone is primarily responsible for the tendon rupture. Perhaps the slight restriction of his activities resulting from the

tendon rupture is an advantage in view of his rising blood-pressure (now 190/120) and poor general condition.—I am, etc.,

M. L. H. LEE.

Nuffield Department of Orthopaedic Surgery, University of Oxford.

SIR,—The case reports by Mr. G. B. Smaill (June 10, p. 1657) and Drs. M. A. Cowan and Suzanne Alexander (p. 1658) of bilateral Achilles tendon ruptures in two patients on steroid therapy prompt me to record the case of a perfectly fit woman of 46 who suffered a similar injury though she had never taken steroids. When running for a bus her left Achilles tendon snapped and she fell. Regaining her feet, she had hobbled only a few steps when the right Achilles tendon ruptured and she fell again. Fortunately this time the bus conductor observed her plight and helped her on to the vehicle; even more fortunately the bus passed her door, and at this point the kindly conductor carried her to the house.

Both tendons had ruptured about 2 in. (5 cm.) above their insertions. Both were sutured the next day and she made a complete recovery, proved by ski-ing 18 months later without pain or difficulty.—I am, etc.,

J. H. MAYER.

Tunbridge Wells, Kent.

Parkinson's Syndrome

SIR,—Recent letters by Drs. R. O. Gillhespy and A. Paton (November 26, 1960, p. 1597) and by Dr. James Robertson (February 4, 1961, p. 363) have suggested that chlorpropamide is of value in the treatment of Parkinson's syndrome. I have myself been investigating the effect of chlorpropamide in the treatment of this condition, and, in particular, have found it useful in controlling tremor. This latter effect has enabled more extensive exercises to be performed by the patients, with additional improvement in their condition and morale. In all cases the dosage was 100 mg. chlorpropamide daily and this was added to the existing therapy. This dosage was not exceeded, since Dr. Robertson has shown that no advantage accrues from increasing the dosage above this level.

The drug was administered to six of a group of twelve patients who were doing group activities. These consisted of exercises and miming. The majority of these patients were taking "artane" (benzhexol hydrochloride) and "norflex" (orphenadrine citrate). If artane was not well tolerated it was replaced with "disipal" (orphenadrine hydrochloride). In patients who suffered from excess salivation small doses of "cogentin" (benztropine methanesulphonate) were used in addition. Most of the patients had found a level of these drugs which varied widely from patient to patient, and which had to a varying extent reduced their symptoms of rigidity and salivation, but none of them derived any benefit from any therapy in the relief of tremor.

It was decided to give them one 100-mg. tablet of chlorpropamide after breakfast. They were instructed to take an extra carbohydrate meal at 10 p.m. Six of a group of twelve patients were found to have marked tremor, and these patients were selected as suitable for a trial of the drug. As a result of a trial lasting for eight weeks, it was found that in four of these patients the tremor was very markedly reduced. In the other there was definite improvement. One patient did not respond, but she was very erratic in her use of the drug, and frequently forgot to use it.

No untoward side-effects have been experienced. We cannot say whether this drug was effective in reducing rigidity, as this symptom was fairly well controlled by other drugs before chlorpropamide was administered. It can be concluded that chlorpropamide is of definite value in the control of tremor associated with Parkinson's syndrome.

I am grateful to Messrs. Pfizer Ltd., who provided the chlorpropamide for this trial.

—I am, etc.,

I. H. K. STEVENS.

Patrixbourne, Near Canterbury, Kent.

Oral Contraception

SIR,—The use of oestrogen type of drugs for control of ovulation in humans would appear risky even under close medical supervision. Little is known definitely of the long-term use of oestrogens in quantities large enough to cause a general hormonal upset such as abolishing ovulation.

Animal experiments do not help, as the administration of oestrogens causes varying effects in different animals and even in different breeds of the same animal. The only naturally occurring oestrogen disease in animals is the "sub-clover" disease of sheep. This is a summation disease which affects merino sheep more than cross-bred sheep, and has no apparent effect on cattle. The oestrogens or pro-oestrogens causing this disease have not been fully investigated, but genistein is present. During the investigation of the disease (which also occurs in guinea-pigs on the same diet) it was found that stilboestrol and oestradiol also produce some of the principal signs—a cystic condition of the endometrium, permanent sterility, and prolapse of the uterus.[1] Experiments with stilboestrol on cattle were discontinued because it led to a form of lesbianism resulting in some cases in fractured pelves.[2] Until a great deal more is known about the summation effect of oestrogen-type drugs over a long period I think it would be unwise to use them for contraceptive purposes. The present methods are fairly effective for family planning, and salpingectomy is safer where future pregnancy is absolutely contraindicated.—I am, etc.,

T. LOVEGROVE.

Wongan Hills, West Australia.

REFERENCES

[1] Bennetts, H. W., *J. Agric. W. Aust.*, 1944, **21**, 104.
[2] Folley, S. J., Scott-Watson, H. M., and Bottomley, A. C., *J. Dairy Res.*, 1941, **12**, 1.

Maternity Units

SIR,—The object of our letter (May 27, p. 1543) had been to express our anxiety about the possible grave effect that might result from the publicity given in the national press to certain phrases from Professor Norman Morris's paper presented to the Royal Society of Health at Blackpool.

It has been pointed out to us that unfortunately the tones in which we wrote implied a criticism of Professor Morris personally, which is quite unjustified by anything contained in his paper, and we wish to take this opportunity of withdrawing such a criticism and apologizing to Professor Morris for having made it.—We are, etc.,

R. G. LAW.
J. MARSHALL SCOTT.

Whittington Hospital, London N.19.

*** We are glad to take this opportunity of saying that there was no intention on our part for the *Journal* to be the vehicle of any criticism of Professor Morris personally. —ED., *B.M.J.*

Ice-packs after Episiotomy

SIR,—In connexion with the correspondence about pain following an episiotomy or a perineal laceration (May 27, p. 1536; June 10, p. 1681), I would like to emphasize a point concerning nursing care of these cases. Since both pain and the danger of sepsis are enhanced by contamination of the wound by the discharges from the uterus, it follows that much unnecessary pain can be avoided if the swabbing of the perineum and the application of clean dressings in preparation for the night is done *after* the baby has been brought to the breast for the last time in the evening.—I am, etc.,

Bristol 9. SYLVIA DICKINSON.

Cervical Carcinoma in a Girl

SIR,—I am afraid that Mr. H. Vincent Corbett's claim (June 10, p. 1682) to have recorded the youngest case of carcinoma of the cervix has been well beaten, for in 1950 Heckel[1] reported two cases of adenocarcinoma of the cervix in girls of 7 and 11 months of age. One of the patients died of the disease on the day of admission, having had vaginal bleeding for a month. The other was surviving normally at the time of the report 21 months after hysterectomy. He records two further cases, one reported by Bumm in a 7-month-old baby in 1909, and one by Scheffey and Crawford in a 22-month-old child in 1932. The condition has yet to be reported in the newborn infant, but doubtless this is only a matter of time.—I am, etc.,

Alder Hey Children's Hospital, Liverpool 12. S. E. KEIDAN.

REFERENCE

[1] Heckel, G. P., *Pediatrics*, 1950, **5**, 924.

Cardiac Arrest in the Consulting-room

SIR,—Dr. Neville A. Silverston (May 20, p. 1439) reports a case of cardiac arrest in a 3-month-old baby following the administration of chloroform for the performance of a circumcision. For the prompt, skilful, and ultimately successful steps that were taken to avert the disaster I have nothing but admiration, but I am still wondering what possible justification there was in 1960 for the administration of chloroform to a 3-month-old baby. We are many years past the hundredth anniversary of the discovery of ether anaesthesia.—I am, etc.,

Hove, Sussex. REX BINNING.

Nitrous Oxide in Dentistry

SIR,—Dr. M. P. Coplans (June 3, p. 1607), in his youthful enthusiasm to debunk his senior colleagues, has got his mechanisms mixed. When his children go blue in the face with rage, they are not suffering from generalized anoxia as are his patients under nitrous oxide with restricted oxygen, but they are showing evidence of local venous engorgement due to obstructed venous return from the face, one of the causes being contraction of the platysma.

He does well to stress the importance of meticulous attention to the air-way and to point the potential danger of "gas/air" analgesia. But if he cared to enlarge his experience by watching more of his colleagues at work, he would find that "the best people" take great pains to prevent breath-holding on intubation or extubation, and, should it occur, take immediate steps to treat it by inflation of the lungs with 100% oxygen.

He lulls himself into a sense of false security by using the term "suboxygenation" which sounds much less horrific than "partial asphyxia." This form of physiological trespass (to use Dr. John Gillies's excellent term) is no less dangerous because it is supervised; and, if its temporary duration does not harm one patient, it may certainly do so to the next if he is one of the large percentage suffering from symptomless restriction of the cerebral circulation due to either atheroma of the carotid and/or vertebral arteries or abnormality of the circle of Willis. If the majority of practising anaesthetists and surgeons did not disapprove of anoxic anaesthesia, then the McKesson technique of secondary saturation would be as popular to-day as it was 30 years ago.—I am, etc.,

London W.4. DONALD BLATCHLEY.

Phenindione and Blood-coagulation Factors

SIR,—Under the above heading Professor P. A. Owren (June 10, p. 1679) and Mr. K. W. Denson (April 29, p. 1205) disagree as to the sensitivity of the thrombotest to Christmas-factor deficiencies. May I be allowed to mention the following regarding this important point?

Without being prejudiced as to the usefulness of the thrombotest in the control of coumarin therapy, the fact that the reagent used therein has a high Christmas-factor activity renders this test insensitive to changes in the level of this factor, irrespective of the concentrations of other blood-clotting factors. I first pointed out this simple deduction[1] in 1959. Subsequently, I carried out experiments which not only confirmed this observation,[2] but also indicated that whatever advantages the thrombotest may offer are most probably due to increased sensitivity to factor VII.—I am, etc.,

Department of Pathology, Southmead Hospital, Bristol. F. NOUR-ELDIN.

REFERENCES

[1] Nour-Eldin, F., *Lancet*, 1959, **2**, 913.
[2] —— ibid., 1959, **2**, 1091.

Hallux Valgus

SIR,—Many must have read Mr. G. N. Golden's article (May 13, p. 1361) on hallux valgus with admiration of the ingenuity of his operative technique. Yet he talks ominously of recurrence. And Dr. C. O. Kennedy (May 27, p. 1543) complains that "physiotherapy and exercises were relegated to four lines in the article and occupy only 'a few weeks after the removal of plaster.'" He goes on to tell us that the orthopaedic surgeons at the Royal London Homoeopathic Hospital "commence physiotherapy before operation, and it is continued during the post-operative period." As an industrial medical officer, a sort of watcher in the wings of the show, I am greatly cheered by Dr. Kennedy's letter. I have sometimes felt exasperated when a worker tells me that the surgeon at the hospital said that when her bunions got bad enough he would operate on them. Also I have had occasionally to treat a foot like a hoof after operation by a distinguished surgeon.

A commencing hallux valgus can be so improved that operation is unnecessary, by mobilizing the whole foot, especially by raising the metatarsal arch and by teaching the patient to walk with it raised, by stretching the capsule of first metatarsophalangeal joint and closing the opened joint below on which she puts her weight at rest and in walking. In industry, for the sake of accuracy of eye and hand, a woman will for long periods take up a stance which is fatal for a sound walking foot. She must be taught that toes are not unnecessary appendages to the foot but part of the plantar arch. She should be encouraged to dance, because in dancing a woman must often walk backwards and she must then hold her foot with more respect for the natural function of the metatarsal arch and the toes. Better still, she should be advised to skate on ice. A woman cannot skate and cock her toes up. She is forced to hold her great toe down in line with the metatarsal, under which line the blade of her skate lies. Hallux valgus is usually accompanied by some loss of power in the peroneals and inability to evert strongly the foot. Skating will strengthen these muscles and improve the stance at work and the walking style. In general feet and hands are not cared for as they deserve.—I am, etc.,

Reading, Berks. E. H. STRANGE.

Strontium-90 in Bone

SIR,—In her letter (May 27, p. 1542) Dr. Frances M. Taylor inquires whether any research on the strontium-90 content of human teeth is being carried out in this country. This subject has been under investigation since 1958 by the director of dental research at the Royal Naval Medical School, Alverstoke, in conjunction with the United Kingdom Atomic Energy Authority Research Station at Woolwich.[1]

In this country it is felt that the analysis of sound permanent teeth which had been calcifying during the years that fall-out has been taking place would be more rewarding than that of deciduous teeth which are either carious or have their roots resorbed and crowns affected by attrition. As the calcification of deciduous teeth in some instances takes place before birth, the placental barrier might also influence the strontium-90 content. Regular samples of third molar and premolar teeth which are extracted in sound condition for orthodontic purposes are still being collected by the Royal Naval Dental Service and six-monthly analyses are supplied by U.K.A.E.A., Woolwich.—I am, etc.,

WILLIAM HOLGATE,
Deputy Medical Director-General (Dental Services) of the Navy.

The Medical Department, The Admiralty, S.W.1.

REFERENCE

1 Bryant, F. J., Henderson, E. H., and Holgate, W., *Brit. dent. J.*, 1960, **108**, 291.

Headache and "Eyestrain"

SIR,—I was interested in Dr. Theodore H. Whittington's letter (June 3, p. 1607), but I would like to point out that I did not state that headache associated with refractive errors is due to wrong glasses; what I did say was I had come across instances where headaches had been caused by a patient wearing incorrect glasses.

I must confess that I have already reached the age of presbyopia, but I cannot remember ever having had a headache which I can trace as being even remotely connected with the necessity for an increase in strength of my presbyopic correction. As far as "decompensated heterophoria" is concerned, of course spectacles which so reduce the latent deviation that the heterophoria becomes fully compensated may entirely relieve the symptoms, of which headache is one of the most frequent.—I am, etc.,

London W.1. T. KEITH LYLE.

SIR,—I wholeheartedly agree with Dr. David Rankine's letter (June 3, p. 1607); too many people wear unnecessary glasses too much. I believe the cost of glasses prescribed on the N.H.S. could be considerably reduced if very small errors of refraction were ignored.

Not only opticians are to blame for such prescribing either. Furthermore, it is not so much the error that is important but the symptoms of which the patient complains. These are so frequently nothing whatever to do with the eyes, although so attributed by the patient.—I am, etc.,

London W.1. J. G. MILNER.

Dermatitis Medicamentosa

SIR,—Dr. C. F. H. Vickers (May 13, p. 1366) uses the term dermatitis medicamentosa to mean "contact dermatitis caused by medicaments." This use of the term is unfortunate because it has always been employed as a synonym for drug eruptions. It is used in this sense in the textbooks by McCall Anderson,[1] Radcliffe Crocker[2], MacLeod,[3] Stelwagon and Gaskill,[4] Ormsby and Montgomery,[5], Sutton,[6] Pillsbury, Shelley, and Kligman,[7] Tobias,[8] and Schwartz.[9] To attempt to change the meaning of an old and well-established term can lead only to confusion.—I am, etc.,

London W.1. E. LIPMAN COHEN.

REFERENCES

1 McCall Anderson, T., *A Treatise on Diseases of the Skin with Special Reference to their Diagnosis and Treatment*, 1894, 2nd edition, p. 360. Griffin, London.
2 Radcliffe Crocker, H., *Diseases of the Skin*, 1888, p. 244. H. K. Lewis, London.
3 MacLeod, J. M. H., *Diseases of the Skin*, 1933, p. 710. H. K. Lewis, London.
4 Stelwagon, H. W., and Gaskill, H. K., *A Treatise on Diseases of the Skin for Advanced Students and Practitioners*, 1921, 9th edition, p. 465. Saunders, Philadelphia.
5 Ormsby, O. S., and Montgomery, H., *Diseases of the Skin*, 1954, 5th edition, p. 225. Kimpton, London.
6 Sutton, R. J., jun., *Diseases of the Skin*, 1956, 11th edition, p. 168. Kimpton, London.
7 Pillsbury, D. M., Shelley, W. B., and Kligman, A. M., *Dermatology*, 1956, p. 876. Saunders, Philadelphia.
8 Tobias, N., *Essentials of Dermatology*, 1952, 4th edition, p. 93. Lippincott, Philadelphia.
9 Schwartz, L., Tulipan, L., and Birmingham, D. J., *Occupational Diseases of the Skin*, 1957, 3rd edition. Kimpton, London.

Sexual Offences Against Children

SIR,—In his interesting letter (June 10, p. 1686), Dr. J. N. Loring asks about the possible effect of publicity on the increase of the above crimes. That there has been a substantial increase is undeniable. Sexual offences (not all of course against children) increased from 5,000 in 1938 to 20,000 in 1959.

I scarcely think that the reporting of sexual crimes *per se* can have any substantial effect in causing an increase in these crimes. It could in fact be argued that such reporting might act as a warning or as a deterrent against such conduct. But I think it is an entirely different matter when promiscuity is glamorized in articles and in plays and films. In my

experience, sexual criminal behaviour is frequently the "end result" of such promiscuity. In promiscuity, of course, the sex instinct continues to be stimulated by fantasy, and therefore can never become fully matured: that is, based upon, and integrated with, the tender emotions. Hence it is most liable to go completely wrong as these fantasies change, and one frequently finds impotence, frigidity, uncontrolled sexual obsession, and criminal sexual tendencies as sequelae.—I am, etc.,

Pinner, Middlesex. ROBERT THOMPSON.

E.E.G.s of Boxers

SIR,—I think I must agree with Dr. F. B. Byrom's remarks (May 6, p. 1323) about the above subject. Dr. J. L. Blonstein may confuse the minds of your readers by referring in his letter (April 22, p. 1174) to irrelevant material. I would again like to stress that if 60% of the boxers showed sporadic bursts of disordered activity, when the records were taken at complete physiological rest (March 25, p. 866), this should at least be considered sufficiently dangerous to discourage youngsters from boxing.

In fact, the Ceylon University authorities were so perturbed by the remarkably high incidence of abnormal E.E.G. changes in our boxers, and also by the appreciable number of students (boxers) who showed changes in their attitude towards work, that the university council decided to ban boxing in Ceylon University. In countries where there are professional boxers there may be plenty of opposition to the banning of boxing, but I feel the time has come to at least ban boxing in schools, universities, and other places of learning.—I am, etc.,

Department of Physiology, Faculty of Medicine, University of Ceylon, Colombo 8, Ceylon R. S. WATSON.

SIR,—I am obliged to Dr. J. L. Blonstein for the missing references (June 3, p. 1611). May I quote, without comment, from the last sentence of one of them ?[1] ". . . Boxing presents the only opportunity in man of observing repeated head injuries in an almost experimental setting."—I am, etc.,

London S.E.5. F. B. BYROM.

REFERENCE

[1] Blonstein, J. L., and Clarke, E., *Brit. med. J.*, 1954, **2**, 1523.

Vaccine Storage

SIR,—With the advent of the warmer weather and the poliomyelitis season, with concurrent requests for protective vaccination, I felt that other doctors with surgeries away from their domestic refrigerator might be interested in my solution to the storage problem.

I acquired a large thermos flask, and filled it three-quarters full with ice (in a polythene bag—which prevents the corners of the cubes from breaking the glass). The ampoules of vaccine I keep in the little blue plastic containers in which one firm sends them out, on top of the ice. By keeping a thermometer in as well, I discovered that the temperature remains about 4° C., and in a cool place remains so about 12 hours after the ice has all melted. The ice is replaced about twice a week, perhaps three times if the weather is very hot.

Smallpox vaccine kept this way also retains its potency for two weeks instead of the usual one.—I am, etc.,

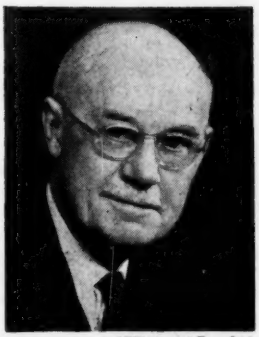
Salford. M. J. DERBYSHIRE.

Obituary

R. C. DAVENPORT, M.B., B.S., F.R.C.S.

Mr. R. C. Davenport, consulting surgeon to Moorfields Eye Hospital, where he was dean of the medical school from 1938 to 1959, died on June 17 at the age of 67. Widely known as an ophthalmic surgeon, Davenport had close contacts with many generations of post-graduate students, for he was also at one time dean of the Institute of Ophthalmology of the British Postgraduate Medical Federation. He was a former president of the Ophthalmological Society of the United Kingdom.

Robert Cecil Davenport, who was born in Chungking, China, in 1893, was the son of C. J. Davenport, F.R.C.S. He was educated at Mill Hill School and at St. Bartholomew's Hospital. He qualified in 1916, and then joined the R.A.M.C. and served as a captain in the first world war. Demobilized in 1920, he returned to his teaching hospital and took the M.B., B.S., London. He gained the F.R.C.S., England, in 1921. After filling the posts of house-surgeon and ophthalmic house-surgeon at Bart's, he was appointed demonstrator of physiology in the medical school and chief assistant in the ophthalmological department of the hospital. He was also Moorfields research scholar at the Royal London Ophthalmic Hospital and ophthalmic surgeon to the East London Hospital for Children. In due course he became a member of the consulting staffs of Moorfields, Westminster, and Central Eye Hospitals. He was a vice-president of the Faculty of Ophthalmology from 1951 to 1954, president of the Section of Ophthalmology of the Royal Society of Medicine from 1955 to 1957, and president of the Ophthalmological Society of the United Kingdom from 1958 to 1960.



[*Elliott and Fry, Ltd.*

Davenport married in 1928 Helen Elizabeth Mayfield, M.R.C.S., L.R.C.P., and they had two sons and a daughter.

H. B. S. writes: Robert Davenport as a man and a doctor was enriched by the possession of many admirable qualities of heart and mind. At a time when more and more elaborate technical diagnostic and therapeutic skills are used in the exercise of some of the special branches of medicine and surgery it was comforting for patients to be served by a doctor such as Davenport, whose warm humanity, genuine sympathy, and understanding constantly dominated the manner in which the cold factual results of modern investigations were presented and who translated these into whatever was reasonable and practicable for the particular patient. His insight and sound knowledge of the background and the likely behaviour of patients of all ages and types influenced the valued advice he gave about their care. Often his gentle diplomacy curbed youthful and ambitious surgical designs on some decrepit old body best left to finish untroubled whatever remained of his or her earthly course.

His patience in clinical practice and in his lucid teaching was infinite. The tolerance he showed of stupidity and the frailties of human nature was remarkable. It was little wonder that he became as a junior teacher in the physiology department at St. Bartholomew's Hospital and later, as a consultant and dean of the medical school at Moorfields, the kindly counsellor and father confessor of generations

of young men from all parts of our dwindling Empire. Such students came to him not only for advice about their studies, but brought to him their domestic problems of landladies, diet, and love. Few men have done so much for good Imperial (Commonwealth) and international relations. He and his wife frequently gave long hospitality in their home to foreigners. His reward lasts in the hearts and affections of a legion of old students in many parts of the world—perhaps the receipt of six model Taj Mahals one Christmas is a slender token of such.

Robert Davenport's sympathy for afflicted mankind showed at its best at St. Dunstan's during the second world war. His firm, sensible, and cheerful guidance of young soldiers through the early trials of the worst of human afflictions was exemplary. Possibly his honest and outspoken distaste and dislike for the political manœuvres that shadowed the background of St. Dunstan's lost him the public recognition he so richly deserved but to which he would have attached, quite characteristically, little importance. His colleagues and patients will always remember him with warmth and genuine affection as a very lovable man and a doctor who brought to his way of life and the practice of his chosen branch of medicine and surgery all that is best of human qualities.

Our sympathy is extended to his widow and family.

Mr. A. G. CROSS writes: Robert Davenport will be mourned by countless numbers of his students in all parts of the world. He was dean of the Moorfields Medical School and of the Institute of Ophthalmology for 21 years, and he was a personal friend to every student who worked at Moorfields during that time. He was also a very real friend to the many St. Dunstaners for whom he was responsible at Church Stretton during the years of the second world war. He was a clinician of great insight, a lucid teacher, and a man who showed much kindness to many people. His outstanding characteristic perhaps was his ability to remember the people he had met. He could recall immediately, by name and in detail, all the students he had known at Moorfields, all the members of St. Dunstan's he had treated, as well as a host of other patients.

CAMILLE GUÉRIN, M.D.

Professor Camille Guérin, who was associated with Professor Albert Calmette in the production of an avirulent strain of tubercle bacillus (bacillus Calmette-Guérin) from which they prepared their B.C.G. vaccine against tuberculosis, died in Paris on June 9. He was 89 years of age. Guérin was born at Poitiers in 1872. He first studied veterinary medicine, and in 1897 he joined the Pasteur Institute in Lille, where Calmette was in charge. It was here, at the turn of the century, that they began their painstaking labours to try to cultivate a strain of bacillus from which a vaccine might safely be prepared. Calmette died in 1933, and only Guérin survived to see the final justification of their work.

The statement by Calmette and Guérin in 1920 that they had succeeded in suppressing the virulence of an originally virulent bovine strain of tubercle bacillus was viewed with scepticism by many bacteriologists. It was suspected that reversion might occur unexpectedly and dangerously. Emotions ran high: for example, the claim by a famous American bacteriologist that dissociation had in fact taken place in his laboratory was answered by the accusation that the virulence was due to a contaminant from his own sputum (he had tuberculosis). Again, the notorious Lübeck disaster in 1930, when a large group of German infants contracted tuberculosis after vaccination, was decided finally to be due to the substitution in error of a human virulent strain kept in the same laboratory as the stock B.C.G. In fact, whether the early B.C.G. cultures did or did not contain some virulent elements, there has been no substantiated evidence of dissociation during the past 30 years at least—during which some 200 million persons have been vaccinated with apparent safety.

After Calmette and Guérin had found that their B.C.G. vaccine could induce a degree of immunity against challenge by virulent mammalian-type *M. tuberculosis* in experimental animals, Weill-Hallé started tests in infants in Paris in 1921. Reports of protection against tuberculosis in further trials in France (some of them undoubtedly exaggerated in their claims and interpretations) were received with doubts in many countries. In Britain, in 1928, Calmette's statistical evidence was strongly criticized by Greenwood in this *Journal*. Thus the global advance of B.C.G. took place very unevenly and painfully, with statistically controlled trials sadly lacking for many years and possible bias entering into many of the published results. However, the accumulation of observations, defective as they often were in design and presentation, were impressively consistent—particularly among contacts in Scandinavia, where the greatest current interest outside France was to be found. Then came the demonstration of the effectiveness of B.C.G. from the properly controlled trials of Aronson and colleagues in North American Indians from 1936 to 1956, and from the unequivocal results of the Medical Research Council trial, from 1950 onwards, in healthy British schoolchildren, the reports of which were published in the *British Medical Journal*. The bacillus Calmette-Guérin has now many daughter-strains in different parts of the world, and their popularity as vaccination material is a lasting tribute to their two indefatigable scientific originators. It is sad that Calmette did not live to see this triumph and fortunate that Guérin did.

After his retirement 18 years ago Guérin lived at the Pasteur Institute in Paris, of which he was honorary director, and continued to take an active interest in its affairs. In 1955 he received the *Grand Prix de la Recherche Scientifique* from the French Academy of Sciences. In 1960 the International Union against Tuberculosis elected honorary members for the first time, and Camille Guérin was one of those upon whom the honour was conferred.

A. P. MEIKLEJOHN, M.A., D.M., B.Sc., M.R.C.P.

Dr. A. P. Meiklejohn's death in a fishing accident on June 14, at the age of 51, has come as a shock to his many friends in this country and abroad. He was senior lecturer in nutrition at the University of Edinburgh. A scientist of distinction, he made important contributions to the literature on his subject, and was joint author, with Sir Stanley Davidson and R. Passmore, of *Human Nutrition and Dietetics*, published in 1959.

Arnold Peter Meiklejohn, son of the late Mr. and Mrs. Meiklejohn, of Harpenden, was born in 1909 and was educated at Gresham's School, where he knew W. H. Auden, Stephen Spender, and John Pudney. From there he went with a science scholarship to Oriel College, Oxford, and graduated B.Sc. in 1931, with first-class honours in physiology. At St. Mary's Hospital, London, he gathered further academic distinctions, including a Radcliffe Scholarship and a Peabody Travelling Fellowship which took him to America for three years, where he worked with several leading physicians, including Castle and Minot. He took the B.M., B.Ch. in 1935, and proceeded D.M. in 1949. During the war he was nutrition adviser to Unrra, and in 1946 he was appointed senior lecturer in nutrition at the University of Edinburgh, which post he held at the time of his death. In 1949 he was elected to Membership of the Royal College of Physicians of London on the record of his published work. His publications were numerous and impressive, in both the British and American literature, and mainly concerned disorders of metabolism. Perhaps the most important was his paper in 1941 in the *Johns Hopkins Bulletin*: "Is Thiamine the Anti-neuritis Vitamin?" In this he courageously challenged the entrenched views of the

time. In 1959 he was joint author with Sir Stanley Davidson and R. Passmore of *Human Nutrition and Dietetics*, which Professor L. J. Witts, in a review in the *British Medical Journal*, called "a major addition to the textbooks of medical science," and which has already become a standard work. Meiklejohn was honorary secretary of the Organizing Committee for the 6th International Congress of Nutrition to be held in Edinburgh in 1963.

C. D. writes: During his 15 years in Edinburgh Peter Meiklejohn assembled a unique reputation; he was not merely another member of the University staff, but was a stimulating, refreshing personality with a delightful eccentricity of view on medicine and most other matters. There was no topic known to physic on which he could not converse; if he thought it significant he would enlarge and illuminate it—if not, his wit soon invested it with an intellectual rigor mortis. Meiklejohn's lectures combined instruction and entertainment in large measure, and, even on subjects which he knew so well, were prepared and rehearsed with the most laborious care. He had many amusing and endearing foibles; there were his oddities of dress, his dilapidated motor-car, his inveterate snuff-taking, and his refusal to drink coffee at lunch as he said it disturbed his post-prandial nap—normally enjoyed on the floor of his room in the Department of Medicine with his head resting on a green velvet pillow specially designed for the purpose.

There can be few doctors in the world—even on the register in Samaria—whose attitude to their fellow men was as compassionate as Meiklejohn's. Even before the days of the National Health Service I have heard him declare that for ethical reasons he could not accept a fee from a patient. This enviable humanitarianism made it nicely appropriate that his lectureship was in nutrition, for his primary interest was not in the diseases whereby men die but in the magic of the substances whereby they live.

The manner of his death while fishing a Highland river was equally inappropriate for a man who kept an electrically controlled aquarium in his study, and brooded with delight over the colours and movements of his specimens, yet found a paradoxical pleasure in their capture. In that same study I found him one night shivering with cold, with his window wide open, because he had admitted and revived an exhausted jackdaw and was leaving it to decide when to resume its journey. He would have had his entire window removed if an albatross had required similar resuscitation.

Peter is dead: we who are left mourn the high tragedy of that death, and grieve for the sorrows of Jean, his wife, who survives him with her two small boys.

M. MANSON, G.M., *M.C.*, M.D., D.P.H.

Dr. Malcolm Manson died suddenly at his home in Southgate on June 1. He was 74 years of age.

Malcolm Manson was educated at Glasgow High School and Glasgow University, where he graduated M.A. in 1907 and M.B., Ch.B. in 1911. After a year as assistant in general practice in Catrine, Ayrshire, he held resident appointments in the Western Infirmary and Royal Infirmary, Glasgow. During two years as senior assistant at the Glasgow Fever Hospital, Ruchill, he took the Cambridge D.P.H. in 1914, and proceeded to M.D. (highly commended) Glasgow in 1920. In 1915 he joined the R.A.M.C. and served for four years in France and Italy attached to the 10th Battalion Queen's Royal West Surrey Regiment. He was awarded the *M.C.* in 1917. In 1920 he was appointed assistant M.O.H., Cumberland, and the following year M.O.H., Whitehaven. From 1928 until he retired from the public health service in 1952 he was M.O.H. of Wood Green, and after 1948 area medical officer for Middlesex County Council. For a number of years he was medical superintendent of the Hornsey, Finchley, and Wood Green Joint Isolation Hospital. During the second world war he was awarded the George Medal in 1940 for rescue work under conditions of great personal danger in which he sustained a spinal injury.

While in Wood Green, Manson was chairman of the North Middlesex Division of the B.M.A. in 1931–2 and a representative at Annual Representative Meetings from 1933 to 1942. He was a member of the Ganglion Club in North London and served his term as president. An honorary life member of the Society of Medical Officers of Health, he was a council member from 1944 to 1946 while president of the Home Counties Branch of the society. After retirement he made several voyages as ship surgeon. He had been a member of the Southgate Group Hospital Management Committee since 1952.

Malcolm Manson brought to bear on his professional duties the fearless courage and kindliness which were the outstanding features of his character. He was not only respected by the members of the numerous public bodies with which he was associated professionally, but was loved by them and above all by his colleagues and his many friends of all ages. He shunned publicity for his work and for himself and preferred the quiet continuous influence of public health workers to the more blatant modern health propaganda. Manson was a great reader and erudite in fields beyond his profession. His library and garden occupied many hours of his days of retirement. He was a charming colleague and will be greatly missed. He is survived by his wife, Dr. Margaret Manson, who is a medical officer, Ministry of Health.—R. P. G.

F. G. FOSTER, M.D., D.P.H.

Dr. F. G. Foster, formerly medical officer of health for Birkenhead, died on April 17. He was 75 years of age.

By the sudden death of Francis Gregory Foster, Birkenhead has lost one of its most popular medical men. Foster was educated at Fettes College and Edinburgh University, where he graduated M.A. in 1907 and M.B., Ch.B. in 1913. He served in the R.A.M.C. from 1914 to 1918, with the rank of major. In 1920 he obtained the D.P.H. (Edinburgh) and was appointed senior resident medical officer at Leicester Isolation Hospital and Sanatorium. In November, 1921, he was appointed assistant medical officer of health for Birkenhead. In 1922 he proceeded M.D. During his years as assistant medical officer of health his work was mainly as venereal diseases officer and tuberculosis officer. Later he became deputy medical officer of health and in 1946, on the retirement of Dr. D. Morley Mathieson, he was appointed medical officer of health for Birkenhead. He retired in 1951.

Foster's medical interests were mainly clinical and his opinion was valued by general practitioners. For some time he served as police surgeon in addition to his other duties. He had the distinction of having a poem published in *Punch*. His classical education was a source of inspiration in many of his witty sayings. He was an ideal colleague and many voluntary organizations found him willing to give assistance. He was keenly interested in boxing, and the North-west Amateur Boxing Association found in him an enthusiastic honorary medical officer. Up to the last he was a keen supporter of and honorary medical officer to Birkenhead Park Rugby Club, and until quite recently it was not unusual to see him acting as touch judge. For many years he was the honorary secretary of the Birkenhead Medical Society, and was one of its most popular members. He was its President for the session 1945–6. His many friends in the profession and among the public mourn the passing of a well-beloved colleague and staunch friend.—R. A. G.

J. W. HIRST, O.B.E., T.D., M.R.C.S., L.R.C.P.

Dr. J. W. Hirst, consultant physician to the Huddersfield Group of Hospitals and to the Storthes Hall Hospital, died on May 27 after a rather prolonged illness. He was 64 years of age.

Joseph Walker Hirst was educated at Huddersfield College, Epsom College, Cambridge University, and King's College

Hospital. He qualified in 1921, and joined his father, the late Dr. Herbert Hirst, in general practice in Huddersfield. He soon became associated with the Huddersfield Royal Infirmary as honorary anaesthetist and later as honorary physician, and he was appointed consultant physician to the Huddersfield Group of Hospitals and to Storthes Hall Mental Hospital when the National Health Service came into being. He served with distinction in both world wars. In the first, as a combatant in the 1/5 Duke of Wellington's Regiment, T.A., he was wounded in November, 1916. After qualifying he served with the same regiment as medical officer, retiring in 1954 with the rank of hon. colonel R.A.M.C. In 1944 he was awarded the O.B.E. (Military Division) for gallant and distinguished service in Italy. At that time he was Assistant Director of Medical Services, Middle East. Previously he had been mentioned in dispatches "for gallant and distinguished service" from November, 1941, to April, 1942.

Apart from his work for the infirmary and his patients, to whom he dedicated his life, Hirst gave much valued service to the community. He served on the Huddersfield Borough Council for ten years, was a former president of the Huddersfield Medical Society, and was chairman of the Huddersfield Division of the British Medical Association in 1928–9. He was chairman of the Huddersfield Executive Council and a member of the Huddersfield Group Hospital Management Committee. He was also chairman of the Huddersfield Workshops and Community Centre for the Elderly.

Those who worked with Hirst mourn a kind and valued colleague, and his patients not only their physician but a friend. He is survived by a widow, to whom we extend our sympathy.—D. G.

JOHN DONALD, M.B., Ch.B.

Dr. John Donald, of Gourock, died in hospital in Glasgow on May 23, after an illness of almost two years' duration. He was 65 years of age.

Jack Donald, as he was affectionately known to his colleagues and friends, came from a well-known Greenock family. His father was a headmaster in one of the local schools. Jack was thus early brought up in an atmosphere of education, and it was no surprise when he distinguished himself both at school and at Glasgow University, where he graduated with honours in 1919. His course had been interrupted by the first world war, in which he served for a time as surgeon probationer in the Royal Navy. After the war he acted in the Western Infirmary as house-surgeon to the late Mr. Archibald Young, who was later to be professor of surgery in succession to Sir William Macewen. In 1922 he entered practice in Gourock and continued there until forced to retire in 1959 through ill-health. By his skill, his conscientious application to his work, and his great interest in, and kindness to, his patients he endeared himself to them throughout the years. These qualities were further enhanced by his innate charm and cheerfulness of manner, and many patients in Gourock have had a deep sense of loss at his passing. In addition to his practice he acted as assistant surgeon at Greenock Royal Infirmary from 1924 until 1943. His ability as a surgeon was well known, both as a diagnostician and as an operator. He also acted as surgeon to the Duncan McPherson Hospital, Gourock, where his administrative abilities were also brought into play.

In his natural self Donald was unusually buoyant. This characteristic of his was infectious and he was much sought after in the social life of the community. He had a keen sense of humour and ready wit and was an accomplished after-dinner speaker. Among his many social activities were president of the Gourock Business Club, president of the Innerkip Society (a benevolent society), a member of the Gourock Golf Club, and many other societies too numerous to mention. He was chairman of the Renfrew and Bute Division of the B.M.A. in 1956–7, a member and past chairman of the local medical committee, and a member of the local hospital board. In summer he loved to holiday on the Isle of Arran at Blackwater Foot, where he was a popular captain of the local golf club. His demise has left a space in the community which is difficult to fill, and we extend our sympathy to his wife, Dorothy, and his two daughters, Dorothy and Pamela.—H. F. K.

J. A. DURANTE, O.B.E., M.R.C.S., L.R.C.P.

The obituary of Dr. J. A. Durante was published in the *Journal* of May 13 (p. 1397).

Dr. H. E. MAGEE writes: I met Durante soon after he came to London with the refugees from Gibraltar, and we had many subsequent discussions about their feeding and nutrition. It was, however, as officers in the Home Guard that I came to know him well and to appreciate his many good qualities. In 1941 I had been placed in medical charge of the 58th (Civil Service, London) Battalion of the Home Guard, and I was very glad when Durante agreed to serve as my assistant, not only because he was a most agreeable colleague, who took his work seriously and was most attentive to his duties, but also because of his knowledge of clinical medicine. I cannot recollect his having missed one of our weekly first-aid classes or any of our field exercises; he was present at every "special invasion" exercise and at all of our camps at Pirbright. Thanks largely to his careful tuition, we had a well-trained body of first-aid workers, and many of them had the satisfaction of putting their knowledge to good use during the air raids of 1944 and more particularly during the flying-bomb period. It was a time of considerable stress for Londoners, and at times of special tension Durante would say with obvious conviction: *Fiat voluntas tua.* It would be true to say that the motto of Aberdeen University fully applied to him: *Initium sapientiae timor Domini.* One afternoon in the summer of 1944 I phoned Durante to arrange for our first-aid class of that evening, but, before we could finish, the warning of immediate danger sounded in my office, but not in his. I ducked under my substantial desk. The bomb passed directly over; I was able to see the sinister thing heading for Kensington. The explosion came in due course and then we finished our conversation. About 20 minutes later he phoned me to say that he could not attend the class that evening—the bomb had hit the home where he lived. His wife and daughter had had a narrow escape from physical injury, but were severely shocked. Durante was badly shaken and the Ministry transferred him straightaway to the Cambridge region, where he remained until he was repatriated in the autumn of 1945. I saw him for the last time as he passed through London, and a sad farewell it was for both of us. He was one of the most likable men I have ever met, and I much regret his passing.

D. CALWELL, M.B., B.Ch.

The obituary of Dr. D. Calwell was published in the *Journal* of June 10 (p. 1692).

Dr. S. GIBSON writes: On reading the obituary of Dr. David Calwell I was taken back in memory to a warm June evening in 1938. The scene was the Great Hall of Queen's University, when I, in company with many more, was anxiously scrutinizing the newly posted pass list for the final examination. My relief at seeing my name on the list must have been apparent. "I see you've passed," said a friendly voice at my side. I perceived a big, genial, kindly looking man, who had obviously been watching. "My name is Calwell," he went on, "I'm going on holiday next week. Will you do a month's locum for me?" So began a friendship which endured over the years, and if ever thereafter I wanted advice or help I always knew to whom I could turn, and never in vain.

I can well remember how, during that month's locum in 1938, Dr. Calwell, well aware of my youth and inexperience, went out of his way personally to ensure my comfort, and frequently would ring me in the evening to ask if I wanted

help or advice. I well remember, too, that when he returned from holiday I informed him that a certain panel patient had left his list, the reason given being that he considered me too young and inexperienced adequately to attend him. Dr. Calwell would have none of this. Vividly I recall how he insisted on my accompaying him to the defaulting patient's house. I recollect that the interview ended, as Dr. Calwell obviously knew it would, with the patient admitting that he had been thinking of changing his doctor for some time and that he had chosen my tenure of office as a suitable pretext. He was forced to concede that he had no complaints against my personal ministration. I recount this incident to exemplify David Calwell's superb loyalty, great good nature, and innate kindliness. These qualities constantly manifested themselves all through the years I knew him.

As you noted, he had a constant yearning for the land. It was only a few months ago, and I was grieved to see that he was then in failing health, that he gave me some excellent advice about the best kind of seed potato I should plant in my garden. It is obvious to those of us who knew Dr. Calwell well that he died as he would have wished, active to the end.

Medical Notes in Parliament

CHEMICALS IN FOOD

[FROM OUR PARLIAMENTARY CORRESPONDENT]

A formidable and familiar indictment on the dangers, latent or suspected, in the use of chemicals during the production, storage, and manufacture of food was presented by Lord DOUGLAS of Barloch to the House of Lords on June 15. Pesticides, herbicides, preservatives, additives; processing, chemical treatment, abstraction of nutritive elements; all these were mentioned in a motion which called for more effective action to protect consumers. It is a topic which Lord Douglas has consistently pursued, and, looking back over 10 years to the first occasion when he expressed concern about it, he found now even greater cause for alarm. Many more chemicals had been brought into common use without adequate knowledge of their effects on human beings; more information had become available to show that chemicals previously thought harmless were in fact dangerous. But very little had been done to safeguard the consumers. On this part of the indictment he quoted the *British Medical Journal* in support. It had recently stated*:

"The effect on human health of 'processing' foods has received scant attention."

and

"The sophistication of foodstuffs has become such a fine art that few of them reach the family table without some chemical treatment designed to improve their appearance, taste, keeping qualities, and ease of preparation."

Inadequate Investigation

The underlying theme of the debate was that not enough was known, and not enough was being done to find out. The ingenuity of manufacturers, Lord DOUGLAS said, had far outrun the vigilance of the authorities who should protect the people's food. To his complaint that the Food Standards Committee had no research staff and no organization of its own Lord KILBRACKEN, an advocate of organic principles in farming, added the point that the British Industrial Biological Research Association, which hoped to start work next year and was financed on a 50:50 basis by the D.S.I.R. and interested manufacturers, had so far been guaranteed only £28,000 a year for five years from the manufacturers.

*December 10, 1960, p. 1723.

One of the suggestions was that the labels on food containers should disclose the exact contents. Those who said this would be incomprehensible or self-defeating did not convince those who believed it would be of value, and Lady SUMMERSKILL illustrated her contention that higher standards were demanded in other countries by reading the lable on a tin of English biscuits sold in Egypt: "Deodorized coconut oil, and palm kernel oil and peanut oil; palm kernel stearine; powdered milk, dried egg, pectin; citric acid, oil of lemon, spirits of wine" followed by named artificial flavours and colourings.

What the Government is Doing

Lord DOUGLAS, calling for more positive action, had said that Ministerial reaction so far had been to appoint more and more committees to advise on one aspect or another. So indeed it seemed when Lord HASTINGS came to reply for the Government, and named seven committees or subcommittees of various sorts before indicating the results expected from their current work. The Research Study Group, investigating the needs for further research into the use of toxic chemicals in agriculture and food storage, is preparing a report expected to be published this year. It is hoped that regulations will be made this year on emulsifying and stabilizing agents, on which the Food Standards Committee reported in 1956, and preservatives, reported on in 1959. The report on bleachers and improvers is now being considered. The Food Additives and Contaminants Subcommittee (formerly the Preservatives Subcommittee of the Food Standards Committee) have reviews in hand on solvents and flavouring agents, and hope to undertake later this year a review of colouring matter. The British list of permitted colouring matter, Lord Hastings mentioned, had been reduced from 80 to 30 (compared with the American list of 15 and the short Continental list), and it would be reasonable to expect a considerable further reduction. There are also to be investigations on nutritional supplements, sequestrants, buffers, and humectants, and substances accidentally introduced in preparing and processing foods, including leaching from wrappers. The Food Standards Committee had considered the disclosure of additives by labelling, and intends to undertake a comprehensive review of the Labelling of Food Order and labelling provisions of the Food and Drugs Act.

Quicker Legislation

Most significant of all Lord Hastings had to say, however, was that it had been agreed that not more than five years should elapse between reviews, and that, in contrast to the considerable delays in implementing original legislation, it was now hoped to keep matters much more up to date and to handle legislation, if it was necessary, within two years of the recommendations being made, instead of four or five.

PUBLICATION OF DOCTORS' NAMES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The demand which recurs at intervals for the publication of names of doctors and dentists from whom a local executive council has withheld payment for breach of contract—in a popular paraphrase "fines on those found guilty of neglect"—was briefly discussed in the House of Commons on June 16. Mr. M. LIPTON (Brixton, Lab.), who raised the subject, said the medical profession was protected by a privileged phalanx of persons and organizations to a degree enjoyed by no other section of the community. The Minister's view that there was a contract between the practitioner and the executive council, to which the patient was not a party, he described as being "from the point of view of the unfortunate victim" specious, dialectic, cynical, legalistic, and heartless. The names should be published not merely as a deterrent to the "guilty" doctor or dentist but for the sake of his other patients, who were entitled to

know what kind of person he was, and it would also be fairer to other doctors in the neighbourhood who came under a cloud of suspicion. The doctor in the Health Service was a public servant, paid out of public funds, and the public were entitled to know who was not doing his job. There were two sides to every case: then let the public hear both sides and all the facts, and it would be to the benefit of all. Justice should be done in the open, not in secret courts in which identities were screened.

Courts, G.M.C., and Service Committees

Miss EDITH PITT, Parliamentary Secretary, Ministry of Health, said the purpose of the service committee investigations was to consider according to statutory rules of procedure whether a practitioner had complied with his terms of service. It was not to decide issues between two parties; the courts were available if a complainant sought damages. Nor was it to punish an offence; this also was for the courts. Nor was it to determine whether a practitioner was fit to practise; this was for the General Medical Council or other professional registration body, and, in relation to the Health Service, the tribunal.

The suggestion that the names of doctors and dentists who suffered withholdings should be published was limited to breaches of the Terms of Service in the Minister's view sufficiently serious to warrant some withholding of remuneration, although if the smallest withholdings were included some of the breaches would be fairly minor. There were objections to this proposal. The strongest reason for the non-publication of names was that the service committee procedure was a matter arising out of the contract, and, so far as the patient was concerned, was in addition to and not in substitution for recourse to the courts, civil and criminal, which was open to any person who thought he had a case for claiming damages or other remedy. Doctors and dentists in the Health Service were in exactly the same position as members of any other profession in this respect. They were not shielded in the way Mr. Lipton had attempted to say.

370 Complaints in 1960

The service committee procedure was part of the administration of the Health Service, and was designed to ensure that the general medical and dental services provided to the public were maintained to a satisfactory standard. The number of cases where remuneration was withheld had tended to diminish in recent years compared with the early years of the Health Service. The number of serious cases was few. There were more than 20,000 general medical practitioners taking part in the service. They were exposed to the scrutiny of their patients throughout their working day, and they must also be ready to answer calls at night. Yet in 1960 only 370 complaints were investigated by the medical service committees throughout England and Wales. and in only 87 cases was the doctor found to have failed to carry out his obligations. Of the 87, 37 were sufficiently serious to warrant the withholding of remuneration, and of these only 18 were in respect of failure to visit or carry out proper and necessary treatment. In the more serious cases it was customary to send particulars of the complaint and investigations to the General Medical Council or General Dental Council for any action they might think necessary.

CHARGES FOR VACCINATION CERTIFICATES

Mr. R. W. SORENSEN (Leyton, Lab.) complained on June 8 of a constituent being charged 7s. 6d. by a doctor for a certificate of vaccination prior to a journey abroad (and incidentally, although there was no complaint on this score, a like sum for signing a passport application). He talked about this being an abuse, by a small minority only of doctors, and suggested an approach by the Ministry of Health to the B.M.A. to advise doctors that such charges should not be made.

A Private Transaction

Miss PITT told him firmly that doctors were under no obligation to provide these certificates, and rejected the suggestion of an approach to the B.M.A. as outside the Minister's province. The 1946 Act provided for regulations to be made "for the issue to patients or their personal representatives by medical practitioners . . . of such certificates as may be prescribed, being certificates reasonably required by them under or for the purposes of any enactment." The International Sanitary Regulations adopted by the World Health Assembly, under which international vaccination certificates were provided as evidence of vaccination, could not be regarded as an enactment for the purposes of the Health Service Acts, and therefore the Minister has no power to prescribe these certificates. There was no statutory provision in the United Kingdom requiring those leaving the country to be vaccinated or inoculated or to obtain a certificate. The doctor was not required to provide them under his terms of service. It was a private transaction, and it was for the doctor to decide what charge, if any, he should make.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on June 3 the degree of D.M. was conferred on G. H. Fairley.

UNIVERSITY OF CAMBRIDGE

Dr. J. T. Fitzsimons, University Demonstrator in Physiology, has been elected into a Fellowship of Gonville and Caius College.

Dr. D. H. Marrian, Ph.D., has been reappointed an Assistant Director of Research in the Department of Radiotherapeutics with tenure from January 1, 1962, for five years.

Dr. M. A. Message has been pre-elected into a Research Fellowship of St. Catharine's College, for research in anatomy.

In Congregation on May 27 the following degrees were conferred:

M.CHIR.—A. G. Norman
M.B.—E. R. Williams, B. E. H. Maden.

UNIVERSITY OF EDINBURGH

At a meeting of the University Court held on May 29 honorary status was conferred as follows: Honorary Lecturer in the Department of Medicine, Dr. M. F. Oliver; Honorary Lecturer in the Department of Psychological Medicine, Dr. W. I. N. Kessel.

The following appointments were announced: Dr. P. G. Gaskell, Lecturer in the General Practice Teaching Unit; Dr. J. H. Turner, Lecturer in Pathology; and Dr. J. R. Smythies, Senior Lecturer in Psychological Medicine.

Mr. D. J. McAuliffe has resigned from his appointment as Lecturer in Ophthalmology, from July 31, 1961.

UNIVERSITY OF LONDON

On April 6 the degree of M.D. was awarded to Julius Lee.

Mr. H. D. Ritchie, Assistant Director of the Surgical Unit at the London Hospital, has been appointed to the University Readership in Surgery, tenable at the London Hospital Medical College.

UNIVERSITY OF BIRMINGHAM

The title of Professor of Neuro-endocrinology has been conferred on John Thomas Eayrs, Ph.D., D.Sc., at present Reader in Comparative Neurology in the Department of Anatomy, from August 1, 1961.

UNIVERSITY OF BRISTOL

Dr. G. S. Makin and Dr. A. K. Yates, Demonstrators in Anatomy, have resigned their appointments.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At an extraordinary meeting of the Council of the College held on June 7, with Sir Arthur Porritt, President, in the chair, Mr. T. A. Ogilvie was admitted to the Fellowship *ad eundem*, and

Surgeon Rear-Admiral D. D. Steele-Perkins was elected to the Fellowship *ad eundem*.

Mr. T. R. Warren, Sir Wilfred Fish, Professor R. A. Willis, Dr. L. Guttman, and Group Captain A. L. Knipe were admitted to the Fellowship of the College without examination as medical practitioners of twenty years' standing.

Diplomas of Fellowship were granted to the following candidates:

J. F. Cogan, W. K. Eltringham, J. Coals, P. Gortvai, J. S. Garfield, W. M. Lennox, N. Ahmed, A. I. Munro, M. O. A. Jaja, B. N. Williams, B. C. McDermott, M. Sharp, P. Atkins, C. P. Monty, B. S. Mather, C. W. Venables, A. I. Friedmann, J. McKenzie, P. P. Reddy, S. C. Banerji, J. J. O'Brien, H. Wickham, A. M. L. Hussein, B. B. Sheaves, A. O. Wilson, I. McI. Duguid, Veronica M. Gammon, J. F. Stone, L. G. Brock, S. B. Chakrabarti, S. Thenabadu, H. A.-B. Alusi, J. L. Godden, R. D. Peduzzi, J. N. McM. Schofield, B. P. Sethi, N. S. Banerji, N. Bhattacharyya, J. C. de Villiers, D. D. Jayawickreme, R. F. Jones, J. H. S. Martin, S. P. Minwalla, A. H. Nakib, J. A. Seddon, I. I. Wilson, G. V. Catford, R. C. Curry, O. W. Deacon, N. R. Hiranandani, W. J. Hughes, R. P. Mittal, P. Chee Nam Wong, D. B. Albuquerque, M. L. Crosfill, H. C. de Castella, R. F. N. Duke, R. K. Dutta, B. Goswami, W. J. Grant, J. D. Jefferies, J. M. Kingsmill-Moore, L. S. Marriott, P. H. Osterberg, J. B. Pearson, R. J. Sellick, J. W. Smith, T. F. Stoyle, R. H. K. Christie, W. A. De Souza, R. J. G. Downie, J. B. Drinkwater, W. N. C. Fraser, A. N. Henry, G. W. Karunaratne, R. S. McKim, J. C. A. Madgwick, K. K. Madhavan, J. D. Maynard, P. J. Millroy, C. J. Moore, B. G. Nadgouda, A. S. Shalom, P. S. Sikand, P. W. Tapsell, R. S. Todd, J. E. Trapnell, M. S. Anand, B. S. Ashby, A. K. Chandra, S. M. Chaudhri, G. A. Chinchanwala, B. P. Cooper, B. A. Crawford, M. M. Das, D. G. A. Eadie, H. B. Griffith, M. H. Heycock, E. G. Ibach, L. Joseph, H. H. Kamdar, I. E. McInnes, N. B. Mehta, M. F. O'Brien, A. Prakash, B. Rabinowitz, R. P. Rosswick, A. P. Singh, Clifford Kwai Kuen Sun, El S. M. Wahb, J. E. Woodyard, Richard Yui, R. A. Ahmed, B. P. Bliss, G. P. Burns, G. J. Coorey, J. C. Doyle, N. A. Matheson, M. D. Middleton, D. A. Patel, R. A. Rieger, T. F. Solanke, J. M. Wynne, A. A. A. Yacoub, J. R. Avrillon, A. C. Cyrus, A. J. Edwards, D. A. Hanania, T. B. Hugh, H. Ludman, R. A. McNeil, N. M. Prabhu, M. R. Rajani, J. D. A. Robb, J. Rudick, E. A. Elebute.

Professor John Bruce, Hon.F.R.C.S., President of the Royal College of Surgeons of Edinburgh, gave an address to the new diplomates who had been successful in the several examinations of the College during the past year.

At a meeting of the Council on June 8, with Sir Arthur Porritt, President, in the chair, Mr. Isaac Wolfson was elected a Member of the Court of Patrons.

The following were co-opted to the Council for the year 1961–2, representing the various branches of practice indicated: *Ophthalmology*, Mr. T. Keith Lyle; *Otolaryngology*, Mr. C. Gill-Carey; Gynaecology and Obstetrics, Mr. H. G. E. Arthure; *Anaesthetics*, Professor W. W. Mushin; *Dental Surgery*, Professor M. A. Rushton; *General Practice*, Dr. John H. Hunt; *Radiology*, Professor D. W. Smithers.

Walker Prizes for their outstanding contributions towards the advancement of knowledge of the pathology and therapeutics of cancer during the period 1955–60 were awarded to Professor Charles Brenton Huggins, Director of the Ben May Laboratories, University of Chicago, and to Dr. Ludwik Gross, of the Cancer Research Unit, Veterans' Administration Hospital, New York City.

The Lady Cade Medal was awarded to Wing Commander James Macconnell Urquhart. The Jacksonian Prize was presented to Mr. Raymond Helsby, of Liverpool; the Hallett Prize to Mr. T. N. Shanmugalingam, of the University of Ceylon; and the Begley Prizes to Miss Susan Kay, of the University of Liverpool, and Miss Rosemary R. Norton, of Guy's Hospital Medical School.

A Diploma of Fellowship was granted to R. N. Gale.

A Diploma of Membership was granted to C. R. Scott.

A Diploma in Orthodontics was granted to J. S. Johnson.

After the meeting a Hunterian Lecture was delivered by Professor I. Ranger on "A Study of the Functional Anatomy of the Diaphragm, with Special Reference to the Aetiology and Treatment of Oesophageal Hiatus Hernia."

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College held on June 2, with the President, Dr. Robert E. Steen, in the chair, the following Members were admitted to the Fellowship of the College: R. W. Barter, A. D. H. Browne, P. J. Crowley, E. A. Martin, H. G. Nelson, G. S. Prince, A. P. H. Randle, J. P. R. Rees.

The following candidates, who were successful in the June examination, were admitted to the Membership: P. J. C. Barry, E. J. Berstock, J. S. Doyle, Elizabeth M. Harpur, D. O'B. Hourihane, Mary P. Kent, A. H. G. Love, R. J. W. Ryder.

ROYAL COLLEGE OF SURGEONS IN IRELAND

The President and Council of the Royal College of Surgeons in Ireland have instituted a Faculty of Radiology in the College, and the following have been appointed to form the first board of the Faculty: *Dean*, Mr. D. J. Riordan; *Vice-Dean*, Dr. S. J. Boland; *Honorary Secretary*, Dr. Finbarr Cross; *Board*, Dr. W. J. McHugh, Dr. D. C. Porter, Dr. T. O'Keefe, Dr. R. A. Reynolds, Dr. J. A. Geraghty, Dr. T. D. O'Farrell, Dr. D. O'Sullivan, Dr. T. P. Eustace, Dr. H. J. Henderson, Dr. E. G. Redman, Dr. J. C. Courtney, Dr. M. J. Brady, Dr. Oliver Chance, Dr. J. J. Magner.

The Faculty will institute courses of postgraduate teaching and will hold examinations for the Fellowship of the Faculty and for the Diploma in Radiology. In the first instance the Council of the College will appoint a limited number of senior radiologists to be Fellows of the Faculty without examination.

Persons who wish their claims to be considered should send full particulars to the Registrar, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin, before January 1, 1962.

ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Fellowship

At a meeting of the general body of Fellows of the College held in Perth on May 1, the following were elected and admitted to Fellowship of the College:

Under Article 44, Kevin Brennan, of Victoria, and W. H. Trethowan, of New South Wales; *Under Article 42*, P. J. Benjamin, W. J. G. Burke, E. D. Burnard, J. H. Deakin, M. L. Edwards, S. E. J. Robertson, T. I. Robertson, and J. N. Sevier, of New South Wales; A. J. M. Dobson, of Tasmania; J. Etheridge and A. C. Schwieger, of Victoria; J. J. Fitzwater, of Queensland; C. Gresson, D. S. Malcolm, I. A. M. Prior, and A. S. Turner, of New Zealand; H. G. Rischbieth, of South Australia.

Membership

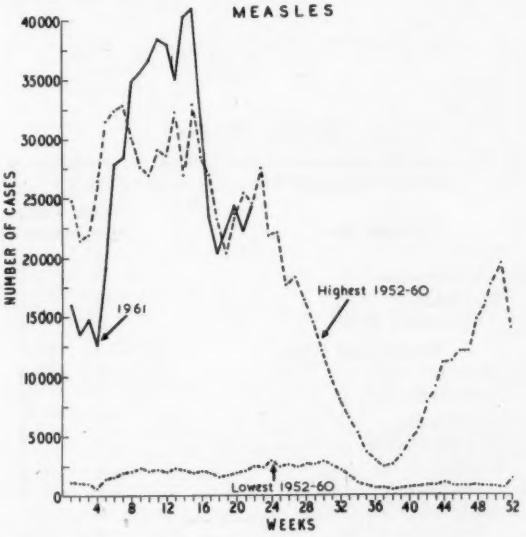
The following candidates, who were successful at an examination held in Australia, were admitted to Membership of the College in April:

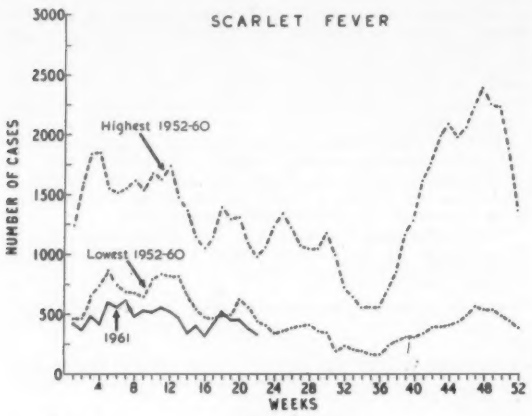
W. Douglas and Ian Ferguson, of Queensland; P. A. Castaldi, E. L. Corlette, R. W. Johnston, B. M. Learoyd, B. P. O'Connell, B. McK. Rush, R. R. Taylor, and I. L. Thompson, of New South Wales; J. P. Carew, J. A. Fuller, June L. Howqua, P. J. Kiernan, A. A. Large, C. R. Lucas, I. G. McDonald, Margery C. McKinnon, Aubrey Pitt, Bernard Sweet, and J. R. York, of Victoria; J. G. Mortimer, of New Zealand; John H. Allison, J. M. Angeloni, E. R. Beech, Michael Duffus, T. M. Gilbert, R. C. Godfrey, Paul Mestitz, W. G. Smith, J. T. Smyth, and T. Waters, of Western Australia.

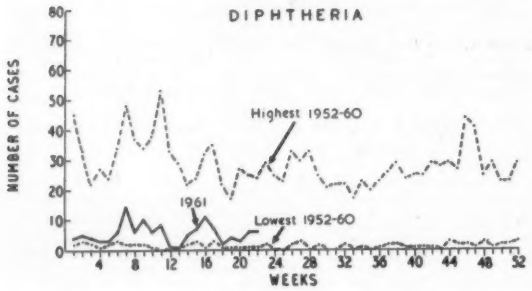
Vital Statistics

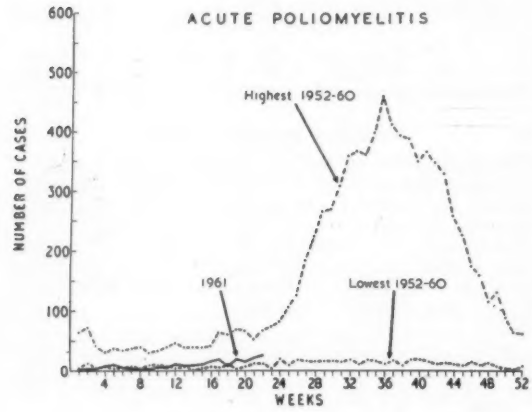
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending June 3	Week Ending June 10
Typhoid Fever		
London	0	1
Hampstead	0	1
Middlesex	0	1
Tottenham M.B.	0	1
Paratyphoid Fever		
Cheshire	1	4
Stockport C.B.	1	4
Hampshire	0	1
Gosport M.B.	0	1
London	1	1
Hackney	1	1
Yorkshire West Riding	0	2
Castleford M.B.	0	2

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **June 3** (No. 22) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961 Eng. & Wales	1961 Lond.	1961 Scot.	1961 N. Ire.	1961 Eire	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire
Diphtheria	6	3	3	0	1	1	0	1	0	1
Dysentery	462	51	152	10	3	1,230	202	175	31	8
Encephalitis, acute	3	0		0		4	0	0	0	
Enteric fever:										
Typhoid	1	0	0	0		3	1	0	0	
Paratyphoid	6	1	4 (B)	0		8	0	0	0	
Food-poisoning	163	14	8	0		200	28	23	4	
Infective enteritis or diarrhoea under 2 years				13	43				26	22
Measles*	24,273	682	364	327	245	2,488	137	38	3	7
Meningococcal infection	17	0	2	0		22	0	17	2	
Ophthalmia neonatorum	21	0	2	0		20	0	1	0	
Pneumonia†	261	19	144	8	1	210	12	135	2	5
Poliomyelitis, acute										
Paralytic	17	0	0	0	2	5	0	0	0	4
Non-paralytic	8	0	2			6	2	0		
Puerperal fever§	184	41	18	0		163	26	13	3	
Scarlet fever	331	35	23	20	5	547	40	49	12	9
Tuberculosis:										
Respiratory	417	77	63	13		423	52	75	17	
Non-respiratory	48	5	13	3		71	8	14	10	
Whooping-cough	441	15	53	2	29	1,483	112	256	14	45

DEATHS	1961 Eng. & Wales	1961 Lond.	1961 Scot.	1961 N. Ire.	1961 Eire	1960 Eng. & Wales	1960 Lond.	1960 Scot	1960 N. Ire.	1960 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	2	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	1	0	0	1	5	0	0	0	0
Influenza	7	1	1	0	1	6	0	1	0	0
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		0	0	0			0	0		
Pneumonia	451	29	30	13	2	403	28	16	10	2
Poliomyelitis, acute	1	0		0	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	62	5	4	2	1	63	6	6	0	2
Non-respiratory		0		0	1		0	0	0	0
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	292	22	27	11	5	275	18	28	2	7
Deaths (excluding stillbirths)	9,602	761	585	120	155	9,148	680	564	103	154
LIVE BIRTHS	16,957	1386	996	316	463	15,413	1281	1051	293	511
STILLBIRTHS	312	31	23			339	21	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Public Health Laboratory Service

The Board which, under the Public Health Laboratory Service Act, 1960—to be brought into force later this year—will take over from the Medical Research Council the administration of the Public Health Laboratory Service is as follows: Sir LANDSBOROUGH THOMSON (*chairman*); Mr. A. H. CLOUGH (formerly Under-Secretary, the Treasury); Professor A. W. DOWNIE, F.R.S. (Liverpool University); Dr. E. HUGHES (M.O.H., Reading); Dr. J. STEVENSON LOGAN (M.O.H., Southend); Mr. J. R. MCGREGOR (formerly Director of Finance, War Office); Professor A. A. MILES, F.R.S. (Lister Institute of Preventive Medicine); Dr. P. A. SMITH (Welsh Hospital Board); Dr. E. T. C. SPOONER (London School of Hygiene); Mr. C. C. STEVENS (I.C.I., vice-chairman Association of Hospital Management Committees); Professor C. STUART-HARRIS (Sheffield University); Dr. D. THOMSON (Ministry of Health); Dr. G. I. WATSON (College of General Practitioners). Mr. D. V. T. FAIRRIE (Medical Research Council) is the Acting Secretary of the Board. From July 3 the address of all branches of the Board's headquarters administrative office will be 24 Park Crescent, London W.1. (Tel.: MUSeum 2223.)

Honour for Professor Khanolkar

Professor V. R. KHANOLKAR, director of the Indian Cancer Research Centre, Bombay, who was last year appointed vice-chancellor of the University of Bombay, is one of the five international scientists chosen by the University of Perugia to receive an honorary doctorate in medicine during the centenary celebrations of the University's chair of morbid anatomy on June 25.

Professor Khanolkar, who was born in 1895, is a graduate of London University and gained his M.D. in 1923. He held professorships of pathology at the Grant Medical College and of pathology and bacteriology at the Seth G.S. Medical College before being appointed director of laboratories and research at the Tata Memorial Hospital in 1941. The Indian Cancer Research Centre, at which he holds his present post, was established in 1952. Professor Khanolkar has filled many international appointments, and holds many international honours, including an Honorary Fellowship of the Royal College of Physicians, Edinburgh, to which he was elected last year.

University of Cambridge Postgraduate Medical School

A new lecture theatre for the Postgraduate Medical School of the University at Addenbrooke's Hospital was opened on June 16 by Lord ADRIAN, O.M., F.R.S., who spoke on "Prospects for Medicine." The Board of Governors of the hospital has made accommodation available at a peppercorn rent to enable the University to build the lecture theatre on the top of the private patients' wing. The opening ceremony was attended by a representative gathering of members of the Council of the Senate, the General Board of the Faculties, the Financial Board, the Board of Examinations, the Council of the Medical School, the Faculty Board of Medicine, the Board of Governors of the United Cambridge Hospitals, the consultant staff, nursing and ancillary staffs, and the local branches of the British Medical Association and the College of General Practitioners. The new accommodation includes a lecture room to seat up to 150 persons and rooms for the nucleus of the Postgraduate Medical Library. The Regius Professor of Physic, Professor J. S. MITCHELL, F.R.S., thanked Lord Adrian for opening the lecture theatre and said that it would fulfil a need which had become increasingly urgent during the past few years.

Turin Congress Awards for Foreign Artists

Dr. E. W. PEET, director of the department of plastic surgery, Churchill Hospital, Oxford, won the premier award for foreign artists at the international exhibition of paintings and sculpture by medical men and women held in Turin earlier this month during the fortnight of international medical and surgical congresses in that city. About 100 medical artists from twelve countries showed works at the exhibition. The Italian and Spanish sections were particularly notable, the former for a number of tranquil abstracts and the latter for the naturalistic portraits by Dr. F. ALVAREZ-DES, who was also a prizewinner. Besides Dr. Peet's prizewinning painting of Brixham Harbour, the British section contained works by Dr. T. ANDERSON, Dr. R. A. BEAVER, Dr. E. BLAKE, Mr. B. BROOKE, Sir PHILIP MANSON-BAHR, Mr. G. PARKER, Dr. A. RACKOW, Dr. R. H. RUSHTON, and Dr. P. TUTTNAUER.

Royal Institute of Public Health and Hygiene Awards, 1961

The Royal Institute of Public Health and Hygiene has awarded the Harben Medal "for eminent services rendered to the public health" to Professor A. BRADFORD HILL, F.R.S., and the Smith Award "to a medical officer of health recognized as having done the most noteworthy work in the discharge of his official duties" to Dr. G. W. H. TOWNSEND, County Medical Officer of Health and Principal School Medical Officer, Buckinghamshire County Council. Both awards are triennial ones.

West London Medico-chirurgical Society

The West London Medico-chirurgical Society, now 79 years old, held its annual banquet at the Zoological Society's restaurant on June 15, under the chairmanship of its President, Mr. HARVEY JACKSON, F.R.C.S. The banquet was well attended by members and their guests. In proposing "The Society," Sir CECIL WAKELEY emphasized the important role of local medical societies as places for free discussion, where "everyone is allowed to say what he thinks." In his reply Mr. JACKSON dwelt on the society's activities during the past year. Dr. W. S. C. COPEMAN proposed the guests, of whom the principal ones were the heads of five sister societies: The Society of Apothecaries (Dr. Charles White), the Hunterian Society (Sir Cecil Wakeley), the Medical Society of London (Mr. Nils Eckhoff), the Harveian Society (Dr. Edward Cullinan), and the Chelsea Clinical Society (Mr. Warren Harvey). Dr. CULLINAN responded for the guests.

Lady Tata Memorial Trust Awards

The Lady Tata Memorial Trust has made, or renewed, the following awards for research on leukaemia and allied diseases in the academic year beginning October 1:

Grants for research expenses: Dr. J. L. AMIEL (France), Cancer and Radiopathology Research Centre, Paris*; Dr. B. M. BRAGANCA (India), Indian Cancer Research Centre, Bombay; Dr. G. W. GRIFFITH (United Kingdom), County Health Department, Anglesey*; Dr. B. LAGERLOF (Sweden), Karolinska Institute, Stockholm*; Dr. H. J. WOODLIFF (United Kingdom), New Pathology Laboratory, Radcliffe Infirmary, Oxford. *Scholarships:* Dr. L. CHIECO-BIANCHI (Italy), Institute of Pathological Anatomy, Bari. (* New award.)

In Brief

New cancer research institutes are being built in Moscow and Leningrad and should be completed next year. Similar institutes are also being built by the Ministries of Health of the Ukraine, Byelorussia, Uzbekistan, and Kazakhstan.

People in the News

▶ Sir ALEXANDER TODD, F.R.S., professor of organic chemistry, University of Cambridge, has been awarded an honorary D.Sc. by Yale University.

▶ Sir WILLIAM COATES celebrated his 101st birthday on June 14. He qualified from the London Hospital in 1881, and has been a member of the B.M.A. for 79 years.

▶ The first award of the J. H. Burn Fellowship at the department of pharmacology, University of Oxford, has been made to Mr. H. P. RANG, M.Sc.Lond.

COMING EVENTS

National Association for Maternal and Child Welfare.—Annual conference, June 28–30, Church House, Great Smith Street, Westminster. Details from the Secretary, Miss I. V. EVELYN, N.A.M.C.W., Tavistock House North, Tavistock Square, London W.C.1.

British Association of Allergists.—Summer meeting, July 1, 11 a.m., department of pathology, Tennis Court Road, Cambridge. Details from Dr. A. W. FRANKLAND, Honorary Secretary, British Association of Allergists, Wright-Fleming Institute, St. Mary's Hospital, London W.2.

Tudor Edwards Lecture.—Dr. J. H. COMROE, "The Pulmonary Circulation and Pulmonary Function," July 5, 5 p.m. See advertisement p. 59.

Society for Endocrinology.—Annual lecture, Sir CHARLES DODDS, F.R.S., "Rime and Reason in Endocrinology," July 5, 5.30 p.m., Royal Society for Tropical Medicine and Hygiene, Manson House, 26 Portland Place, London W.1. Chairman: Professor E. C. AMOROSO, F.R.S. Free, without ticket.

Institute of Obstetrics and Gynaecology, London University. — General practitioners' lecture-discussion, "Antepartum Haemorrhage," July 11, 8.30 p.m., in the Institute, Queen Charlotte's Maternity Hospital, Goldhawk Road, London W.6.

University of London.—Professor R. L. RILEY (associate professor of medicine, Johns Hopkins School of Medicine), "Interrelations Between Breathing and Blood Flow," July 17, 4 p.m., Middlesex Hospital Medical School, Mortimer Street, London, W.1. Chairman: Professor A. KEKWICK. Admission free, without ticket.

University of London, British Postgraduate Medical Federation, Institute of Psychiatry.—Special course in practical neurochemistry, September 18–22. See advertisement p. 59.

University of London, British Postgraduate Medical Federation, Institute of Psychiatry.—Symposium for consultants, "The Future of the Mental Hospital," October 5, 6. See advertisement p. 58.

South-western Obstetrical and Gynaecological Society.—Autumn meeting, Portsmouth, November 7–10. See advertisement p. 58.

NEW ISSUES OF SPECIALIST JOURNALS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.*1.

JOURNAL OF CLINICAL PATHOLOGY

A Clinicopathological Study of Benign Hodgkin's Disease. P. J. Dawson and C. V. Harrison.
Tumours of Salivary Tissue. J. Malcolm Cameron.
An Assessment of the Anatomical Factor in Cor Pulmonale in Emphysema. M. S. Dunnill.
Nocardiosis in Anaemic Patients Given Steroids. D. N. Whitmore, G. A. Gresham, and M. J. Grayson.
A Family Study of the Biochemical Defects in Wilson's Disease. J. F. Soothill, J. D. Blainey, F. C. Neale, M. Fischer-Williams, and S. C. Melnick.
A Study of Six Representative Methods of Plasma Bilirubin Analysis. Derek Watson and Janice A. Rogers.
Hypercholesterolaemia and Diabetes Mellitus. J. N. Harris-Jones and D. J. Ward.
Multiple Plasma Enzyme Activities in Liver Disease. T. Hargreaves, I. Janota, and M. J. H. Smith.
Soluble Cerebral Proteins in Normal and Oedematous Brain. J. N. Cumings.
The Usefulness of Counting "Heat-affected" Red Cells as a Guide to the Risk of the Later Disappearance of Red Cells After Burns. Elizabeth Topley.
The Distribution of Blood Cells on Haemacytometer Counting Chambers, with Special Reference to the Amended British Standards Specification 748 (1958). C. Sanders and D. W. Skerry.
The Defect of Blood Coagulation in Joints. A. J. Harrold.
A Latex Fixation Test Using British Latex and Bovine Gamma Globulin. R. B. Payne.
The Testing of Sterilizers: 2 Thermophilic Spore Papers. J. C. Kelsey.
Technical Methods
An Apparatus for Measuring the Tensile Strength of Blood Clots. R. G. Macfarlane and A. H. Tomlinson.
An Automatic Staining Machine for Blood and Marrow Films on Slides. J. G. Selwyn.
The Association of Clinical Pathologists: 66th General Meeting.
Book Reviews.

Volume 14. No. 3. (Bi-monthly; £4 4s. annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

Neuroretinopathy Following Haemorrhage, with a Discussion on the Nature of Cytoid Bodies. N. Ashton, M. A. Pears, and G. W. Pickering.
"Spider Lick." An Epidemic Ophthalmo-dermatozoosis due to Beetles of the Genus *Paederus*. E. J. Somerset.
Occurrence in Rodents of Reversible Drug-induced Opacities of the Lens. W. Weinstock and H. C. Stewart.
Monosemicarbazone of Adrenochrome (Adrenoxyl) and Cataract Surgery. H. T. Swan, A. B. Nutt, G. H. Jowett, W. J. Wellwood Ferguson, and E. K. Blackburn.
Inner Limiting Membrane of the Retina. C. Pedler.
Role of the Sympathetic in Lacrimal Secretion. J. Whitwell.
Neuroblastoma Presenting as Ecchymosis of the Eyelids. D. J. Wilson.
Notes.

Volume 45, No. 6. (Monthly; £6 annually, £9 with *Ophthalmic Literature* and Index.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 26

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Sodi Pallares: A New Classification of Myocardial Infarction.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. Severo Ochoa: Propionic Acid Metabolism in Animal Tissues.

Tuesday, June 27

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. B. M. Ansell: Problems of Psoriasis and Arthritis.

Wednesday, June 28

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Bacteriology in Diseases of the Skin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: Congenital Abnormalities of the Thoracic Cage, Lungs, and Pulmonary Arteries.
LEWISHAM GENERAL HOSPITAL.—5.45 p.m., Mr. S. M. Cohen: Physiopathology of Peripheral Vascular Disorders.
MEDICAL RESEARCH COUNCIL.—At National Institute for Medical Research, Mill Hill, London N.W., 5 p.m., Dr. Severo Ochoa (New York): Biosynthesis of Ribonucleic Acid.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. H. J. Parish: Prevention of Tetanus.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arnott Demonstration by Miss J. Dobson: John Hunter's Animals and Friends.
WHITTINGTON HOSPITAL.—11.30 a.m., Sir Adolphe Abrahams: Pitfalls in Some Gastroenterological Symptoms.

Thursday, June 29

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Mr. A. K. Monro: Malignant Melanoma.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., annual general meeting.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Sodi Pallares: Electrocardiographic Approach in Congenital Heart Disease.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Denis Williams: postgraduate demonstration in neurology.

Friday, June 30

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. I. Hill: clinical demonstration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. J. A. Shepherd: Some Unsolved Problems in the Management of the Acute Abdomen.
ROYAL SOCIETY OF HEALTH.—At Hoare Memorial Hall, Church House, Westminster, London S.W., 2.30 p.m., Mr. G. Birch-Lindgren, Hon.F.R.S.H. (Stockholm): Design for Health Living.

Saturday, July 1

SHEFFIELD REGIONAL PSYCHIATRIC ASSOCIATION.—At Kingsway Hospital, Derby, 11 a.m., annual general meeting. Dr. D. Macmillan and Professor E. Stengel: Report on the 3rd International Congress in Montreal.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Quamina.—On May 9, 1961, at St. Woolos Hospital, Newport, to Dr. Elizabeth (formerly Smith) and Dr. David Quamina, a son—John David.
Whimster.—On June 4, 1961, in Fiji, to Sybil (formerly Wallace), wife of W. F. Whimster, M.B., B.Chir., a daughter—Claire Elizabeth.

DEATHS

Caldwell.—On June 5, 1961, at Epsom District Hospital, Epsom, Surrey, William Alexander Caldwell, M.R.C.P., D.P.M., of 15 Ashdown Road, Epsom.
Carter.—On June 6, 1961, at Wincanton Memorial Hospital, Wincanton, Som., Ruth Tayspill Carter, M.B., B.S.
Connell.—On June 3, 1961, at his home, Acorn Bank, Wetheral, Carlisle, Cumberland, Richard Connell, M.B., B.Ch., B.A.O., F.F.R., Surgeon Commander, R.N., retired, aged 79.
Cubbon.—On June 5, 1961, at his home, Glen Robin, Port Erin, Isle of Man, Henry Thomas Cubbon, M.B., Ch.B., D.M.R.E..
Felton.—On June 3, 1961, at Springfield Hospital, Grimsby, Lincs, Edgar Hall Felton, M.B.E., M.R.C.S., L.R.C.P., of 16 Cumberland Avenue, Grimsby, aged 84.
Hazra.—On June 7, 1961, in hospital, the result of an accident, Arun Kumar Hazra, M.B., of Astley, Tyldesley, Manchester.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Impending Menopause

Q.—*For the past six months the interval between the periods of a woman aged 47 has varied from 16 to 35 days. She wishes to continue to practise the "safe period" method of preventing conception (she has five children). Is there any hormone therapy which will regulate her periods, or should these presumably menopausal irregularities be left untreated?*

A.—Since ovulation is related in time to the date of onset of the next period, such wide variations in menstrual cycle make it very difficult if not impossible to determine the "safe period." At this lady's age such wide variations should not be regarded as a normal premenopausal phenomenon, but she should be referred for full gynaecological examination, including diagnostic curettage. But even if no abnormality is found, it is doubtful whether it is wise to try to regulate the cycle with hormone therapy at a time when the menopause is probably impending. It would be better to resort to a mechanical form of contraception as being safer, even though it is likely that at the age of 47 such irregular menstruation is anovular.

Intervals Between Combined Vaccine Doses

Q.—*What interval may elapse between the second and third injection of diphtheria pertussis vaccine and diphtheria pertussis tetanus vaccine in infancy without a new series being undertaken? Is a third injection of either of these two prophylactics of any use after one year?*

A.—The interval between the second and third doses of combined vaccines such as diphtheria and pertussis vaccine or diphtheria, tetanus, and pertussis vaccine is less important than the interval between the first and second doses, but should not be more than three months, and it should be extended beyond two months only if the first two doses have been properly spaced (four to six weeks apart). If more than two months elapse between the first two doses, or more than three months elapse between the second and third dose, it would be advisable to start the course afresh. A third injection one year after the second would not have the desired effect, and should be considered as the first dose of a new course.

Milk and Eczema

Q.—*A man who has had psoriasis for 17 years without intermissions now appears to be cured. His cure has coincided with drinking goat's milk during the past two months. Is goat's milk known to be of value in this condition or in various forms of eczema?*

A.—The disappearance of psoriasis, present without remission for 17 years, after drinking goat's milk for two months can unfortunately be only a coincidence, and it would indeed be unwise to consider this patient's present satisfactory condition as more than a temporary phase. There is, at this stage, no evidence that psoriasis is related to any specific hypersensitivity, allergic or otherwise, to cow's milk or that it is due to any dietary deficiency made good by drinking goat's milk.

It has been stated frequently that widespread infantile eczema occurs more frequently in bottle-fed than in breast-fed babies, and that substituting goat's milk for cow's milk has been beneficial. I am not aware of any unassailable evidence supporting this thesis. Allergy to foods usually gives rise to alimentary symptoms and urticaria, but rarely, if ever, to widespread eczema. Although many dermatologists maintain that food allergy does not cause eczema, except when giving rise to allergic contact sensitivity, it would, I feel, be unwise to deny that this can occur. But before accepting any clinical phenomenon as being due to an allergic mechanism, sound evidence should be obtained by scientific experiments, including carefully conducted and interpreted intradermal skin tests, the demonstration of the appropriate antibodies in the tissues or in the serum, and stringent dietary tests.

Persistent Herpes Simplex

Q.—*A girl aged 20 has had a herpes simplex eruption on the cheek for two years. Topical corticosteroids suppress it, but of all the treatments (including oral antibiotics) only "virugon" appeared effective, but the eruption recurred when the dose was reduced on the seventh day. (1) Can virugon be given without toxicity over a long period? (2) What other treatment is there? (3) May topical steroids spread the infection?*

A.—While recurrent herpes simplex of the lips and perioral area is not infrequent, a herpes simplex eruption affecting the cheek continuously for two years must be very rare indeed. However, if there are grouped vesicles on an erythematous base there can be little doubt about the diagnosis.

The quite non-specific anti-inflammatory effect of topical corticosteroids usually hastens the disappearance of the lesions, and apparently there is no risk of spreading the infection with this treatment except in herpetic keratitis, where topical corticosteroids should never be used. Little is known about the toxic effects of long-term treatment with virugon, and before treating even such a persistent attack of herpes simplex with an oral drug about which our knowledge is still very limited[1] other local treatments should be tried. Drying applications are essential, and ointments or creams should not be used. Silver nitrate 0.25% or 0.5% solution applied twice daily is often quickly successful; "siccolam 'B'" is another helpful drying application.

If these local simple measures should not produce rapid disappearance of the eruption, a thorough search should be made for precipitating internal and external factors.

REFERENCE

[1] *Brit. med. J.*, 1961, **1**, 48.

Fluoride in Sea-water Salt

Q.—*I have been told that people in the Middle East attribute their good teeth to taking salt in their diet in the form of evaporated sea-water salt. Is it possible that sea-water salt contains sufficient fluoride to prevent dental caries?*

A.—It is generally agreed that a daily intake of slightly more than 1 mg. of fluoride, supplementary to that in foods in a typical West European or North American diet, is optimal to prevent caries. This can be provided by artificial fluoridation of the water supplies at a level of 1 p.p.m.

It is unlikely that the consumption of salt in this country contributes materially to the daily intake of fluoride. Chemical analysis of four random samples of salt purchased in this country in the form of packet table salt, lump cooking salt, loose common salt, and reagent sodium chloride, kindly undertaken by Dr. H. L. Bolton, of the Laboratory of the Government Chemist in London, showed[1] that they contained less than 4 p.p.m. of fluoride.

The composition of sea-water suggests that evaporated sea-water salt will contain about 40 p.p.m. of fluoride. It would be expected, therefore, that at least 30 g. of evaporated sea-water salt would have to be consumed each day to provide an optimal supplement of fluorides for adults, assuming some loss during cooking. Statistics from Switzerland[2] suggest that the average intake of domestic cooking salt, not including salt in bread, manufactured soups, etc., is about 5 g. per day for adults. Allowing for the dry, hot climate of much of the Middle East, and a decreased use of manufactured foods compared with Europe, the fluoride

intake in salt may provide a small but not necessarily insignificant addition towards an optimal intake of fluoride, especially if much fish is eaten. Probably, however, the relative lack of refined foods and less eating between meals in the Middle East is largely responsible for the lower incidence of caries.

The controlled incorporation of fluorides at a level of 100 parts per million in cooking salt has been advocated[2] in Sweden and is now used in some parts of Switzerland,[3] but usually provides only about one-third of the optimal supplement of fluorides.

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1 Bolton, H. L., personal communication, 1961.
2 Aeppli, H., *Gynaecologia (Basel)*, 1959, **148**, 111.
3 Santesson, G., *Odont. Revy*, 1957, **8**, 345.

Prolonged Androgen Therapy

Q.—*Is prolonged androgen therapy in a young man aged 30, especially with the new long-acting hormones, likely to cause irreversible depression of the gonadotrophic hormones? If so, what products are available to counteract this?*

A.—Unless the patient referred to is a eunuchoid, there would seem to be no justification for long-term androgen therapy. If he is, due to primary hypogonadism (an intrinsic testicular defect), then depression of gonadotrophic hormone production by the pituitary is of no consequence. If the hypogonadism is due to gonadotrophic insufficiency, then the question of suppression will not arise. In other words, if the androgen therapy is justified, the effects on gonadotrophin production are of no importance. In any case, gonadotrophin depression would not be irreversible.

Serous Discharge from Nipple

Q.—*A nulliparous widow, aged 47, has during the last few weeks noticed a slight intermittent serous discharge from the left nipple; there are no obvious signs or symptoms, the breast being free from any discernible abnormality. What significance should one attach to the serous discharge, and what further action, if any, is indicated?*

A.—Opinions seem to vary on the significance of a slight serous discharge from the nipple in cases where clinically the breast appears quite normal. It is usually agreed, however, that a clear discharge can occur in cases of chronic mastitis and sometimes other benign lesions. If the discharge can be seen to come from a particular duct gentle pressure over the areola of this sector may produce further fluid from a dilated duct. At times the discharge may be so slight as to cause a mere "crusting" over the nipple.

Such cases require no active treatment but should be kept under observation. Of course, if the discharge becomes pink-tinged, or be of actual blood—in the absence of trauma—a duct papilloma or carcinoma is present, and active measures are immediately required. The skin of the nipple, too, should be watched, for occasionally crusting may be the first sign of Paget's disease of the nipple.

The writer has, however, followed many cases like the one mentioned in the query for several years without seeing the development of any untoward change.

Lupus Erythematosus and Arthritis

Q.—*Does lupus erythematosus produce multiple arthritis, and, if so, what are its characteristics?*

A.—Systemic lupus erythematosus does produce a polyarthritis, which may be indistinguishable from rheumatoid arthritis. On most occasions, however, there is more systemic upset, and pains are between joints as much as in them. There may be much discomfort but little in the way of objective physical signs. It is this discrepancy between symptoms and signs which is one of the essential differences between rheumatoid arthritis and S.L.E. The histological differences have been described by Cruikshank.[1]

REFERENCE

1 Cruikshank, B., *Ann. rheum. Dis.*, 1959, **18**, 111.

NOTES AND COMMENTS

Sensitivity to Barbiturates.—Dr. M. M. GLATT (Southall, Middx.) writes: The question whether addiction to a barbiturate is less harmful than alcoholic addiction ("Any Questions?" April 1, p. 979) is of great practical importance in the treatment of alcoholics, many of whom suffer from insomnia and urgently ask the doctor for hypnotics—as a rule for barbiturates. Certain types of alcoholics quickly also become dependent on barbiturates, taking them to excess while still drinking, or substituting barbiturate habituation or addiction after having given up alcohol. The risk of barbiturate habituation and addiction seems in our experience much greater in the man who has become an alcoholic chiefly for psychological reasons, such as emotional conflicts (Jellinek's "alpha alcoholic"[1]), than in the predominantly "occupational" alcoholic. There is so much resemblance between barbiturate addicts and certain types of alcoholics that they often fit readily into the same psychotherapeutic group. Apart from possible habituation and addiction, there are also the dangers of suicidal or accidental overdosage, both risks to which alcoholics are particularly prone. The possible potentiation of the effects of alcohol and barbiturates[2] should be kept in mind: of approximately 300 fatal cases in this country in 1960 of accidental poisoning by barbiturates, about one in six was associated with alcohol consumption (April 29, p. 1262). Alcoholic patients who in the past had also taken drugs to excess gave a number of reasons why they had come to prefer drugs to alcohol and why it had "paid" to replace alcohol by drugs. Among the reasons given it was mentioned that a smaller amount of drugs had sufficed to transport them into the desired "wonderful dream-world"; that "drugging" was a more rapidly effective and cheaper way and could be achieved with the help of the N.H.S.; that their breath did not give them away if watched by suspicious relatives; and that they did not appear so "dirty." A minority of alcoholics dread drugs, stating that they felt it was too dangerous to take overdoses in a drunken state, or that drug-taking was not a "social" act and there was less "fun" in it than drinking—as one alcoholic woman put it, "like taking pills secretly in place of a meal in company." Whereas the development of alcoholics into drug addicts seems quite common, the reverse happening of barbiturate addicts becoming alcoholics seems uncommon. The only explanation of the rarity of this phenomenon that could be obtained from addicts was the feeling that alcohol was less potent than the drugs ("chicken feed"). In the treatment of alcoholics, hypnotics will often be necessary, but should be used sparingly. Non-barbiturates seem to be preferable to barbiturates, though they too are not completely free from risks—e.g., glutethimide—recommended in your leading article (May 6, p. 1306)—has rarely been found to produce habituation and addiction.[3,4]

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1 *Lancet*, 1961, **1**, 651.
2 *Brit. med. J.*, 1953, **1**, 1269.
3 Glatt, M. M., ibid., 1959, **1**, 50.
4 Rogers, G. A., *Amer. J. Psychiat.*, 1958, **115**, 551.

OUR EXPERT replies: Dr. Glatt's extension to my answer is very useful. It should be remembered that non-barbiturate hypnotics, such as glutethamide, have been introduced into medical practice much more recently than the barbiturates, and have not had the same opportunities of producing habituation and addiction—yet.

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